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(54) Titre : PROCEDES ET MATERIAUX POUR AUGMENTER LES NIVEAUX DE POLYPEPTIDES EB DE FACTEUR DE
TRANSCRIPTION

(54) Title: METHODS AND MATERIALS FOR INCREASING TRANSCRIPTION FACTOR EB POLYPEPTIDE LEVELS

(57) **Abrégé/Abstract:**

This document provides methods and materials for increasing TFEB polypeptide levels. For example, compounds (e.g., organic compounds) having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, formulations containing compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for making compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for making formulations containing compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for increasing TFEB polypeptide levels within cells and/or within a nucleus of cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels are provided.



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(54) Title: METHODS AND MATERIALS FOR INCREASING TRANSCRIPTION FACTOR EB POLYPEPTIDE LEVELS

(57) Abstract: This document provides methods and materials for increasing TFEB polypeptide levels. For example, compounds (e.g., organic compounds) having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, formulations containing compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for making compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for making formulations containing compounds having the ability to increase TFEB polypeptide levels within cells and/or within a nucleus of cells, methods for increasing TFEB polypeptide levels within cells and/or within a nucleus of cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels are provided.

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METHODS AND MATERIALS FOR INCREASING TRANSCRIPTION FACTOR EB POLYPEPTIDE LEVELS

CLAIM OF PRIORITY

This application claims priority to U.S. Patent Application Serial No.
5 62/788,049, filed on January 3, 2019, and U.S. Patent Application Serial No.
62/879,374, filed on July 26, 2019, the entire contents of which are hereby
incorporated by reference.

FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with government support under grant number
10 1R35HL139860 and 1R01HL142777 awarded by National Institutes of Health (NIH).
The government has certain rights in the invention.

TECHNICAL FIELD

This document relates to methods and materials for increasing transcription
factor EB (TFEB) polypeptide levels. For example, the document provides
15 compounds (e.g., organic compounds) having the ability to increase TFEB
polypeptide levels within cells, formulations containing compounds having the ability
to increase TFEB polypeptide levels within cells, methods for making compounds
having the ability to increase TFEB polypeptide levels within cells, methods for
increasing TFEB polypeptide levels within cells, and methods for treating mammals
20 (e.g., humans) having a condition responsive to an increase in TFEB polypeptide
levels.

BACKGROUND

Lysosomes are membrane-bound cellular organelles that contain a variety of
digestive enzymes responsible for metabolism and degradation of various
25 biomolecules, such as proteins, lipids and nucleic acids, which are either damaged or
no longer needed by the cell. In the absence of functional lysosomes, undegraded
molecules rapidly accumulate within the lysosome and subsequently in the cytoplasm,
leading to cellular damage and contributing to a number of pathological conditions.

TFEB is an important transcription factor that regulates the expression of
30 hundreds of genes that control autophagy, lysosome biogenesis, and lipolysis

(Sardiello *et al.*, *Science*, 325(5939):473-7 (2009); and Wang *et al.*, *Nat. Commun.*, 8:2270 (2017)). When TFEB translocates from the cytoplasm of a cell to the nucleus, it activates expression of its target genes, which was shown to induce lysosomal biogenesis and increase the degradation of complex molecules including glycosaminoglycans and pathogenic protein aggregates such as those involved in Huntington's disease, Parkinson's disease, and Alzheimer's disease (Sardiello *et al.*, *Science*, 325(5939):473-7 (2009); and Napolitano *et al.*, *J. Cell Sci.*, 129:2475-2481 (2016)). Several small-molecule activators of TFEB were shown to be useful for treating metabolic and age-related disorders (Wang *et al.*, *Nat. Commun.*, 8:2270 (2017)).

SUMMARY

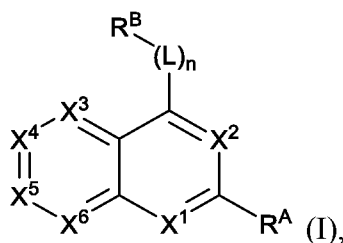
This document provides methods and materials for increasing TFEB polypeptide levels. For example, the document provides compounds (e.g., organic compounds) having the ability to increase TFEB polypeptide levels within cells, formulations containing compounds having the ability to increase TFEB polypeptide levels within cells, methods for making compounds having the ability to increase TFEB polypeptide levels within cells, methods for making formulations containing compounds having the ability to increase TFEB polypeptide levels within cells, methods for increasing TFEB polypeptide levels within cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels. This document also provides compounds (e.g., organic compounds) having the ability to increase TFEB polypeptide levels within the nucleus of cells, formulations containing compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for making compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for making formulations containing compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for increasing TFEB polypeptide levels within the nucleus of cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels within the nucleus of cells.

As described herein, the compounds provided herein can be used to increase TFEB polypeptide levels within cells *in vitro* or *in vivo* and/or within the nucleus of cells *in vitro* or *in vivo*. For example, the compounds provided herein can be used to

increase the nuclear polypeptide levels of endogenously produced TFEB polypeptide within cells of a mammal (e.g., a human). In addition, the compounds provided herein can be used to treat mammals (e.g., humans) having a disease, disorder, or condition associated with a low cellular and/or nuclear level of TFEB polypeptides.

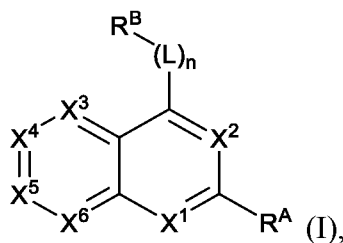
5 In some cases, the compounds provided herein can be used to treat mammals (e.g., humans) having a disease, disorder, or condition that is responsive to an increase in TFEB polypeptide levels within cells and/or within the nucleus of cells.

In some embodiments, this document provides a method for increasing TFEB polypeptide levels within a cell and/or within the nucleus of a cell. The method
10 comprises (or consists essentially of or consists of) administering, to a mammal (e.g., a human) containing the cell, a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^A , R^B , L , and n are as described herein. In some cases, the administering step can
15 result in an increase in the TFEB polypeptide level within the nucleus of the cell as compared to the TFEB polypeptide level within the nucleus of the cell before the administering step.

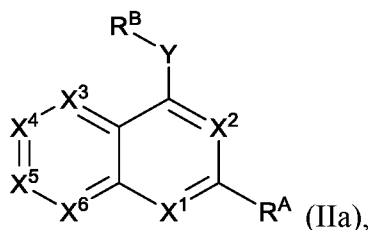
In some embodiments, this document provides a method for treating a disease, disorder, or condition selected from the group consisting of lysosomal storage
20 diseases (LSDs), acute or chronic inflammatory disorders, neurological diseases, and conditions of age-related functional decline in a mammal (e.g., a human). The method comprises (or consists essentially of or consists of) administering, to a mammal (e.g., a human) having the disease, disorder, or condition, a compound of Formula (I):



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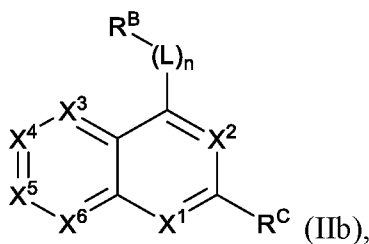
or a pharmaceutically acceptable salt thereof, wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^A , R^B , L , and n are as described herein. In some cases, the administering step can reduce the severity of a symptom of the disease, disorder, or condition. In some cases, the administering step can result in an increase in the TFEB polypeptide level within the nucleus of a cell of the mammal as compared to the TFEB polypeptide level within the nucleus of the cell before the administering step.

In some embodiments, this document provides a compound of Formula (IIa):



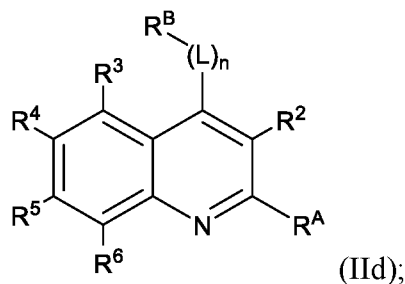
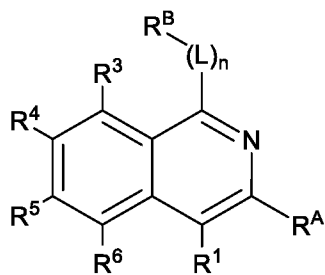
or a pharmaceutically acceptable salt thereof, wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^A , R^B , and Y are as described herein.

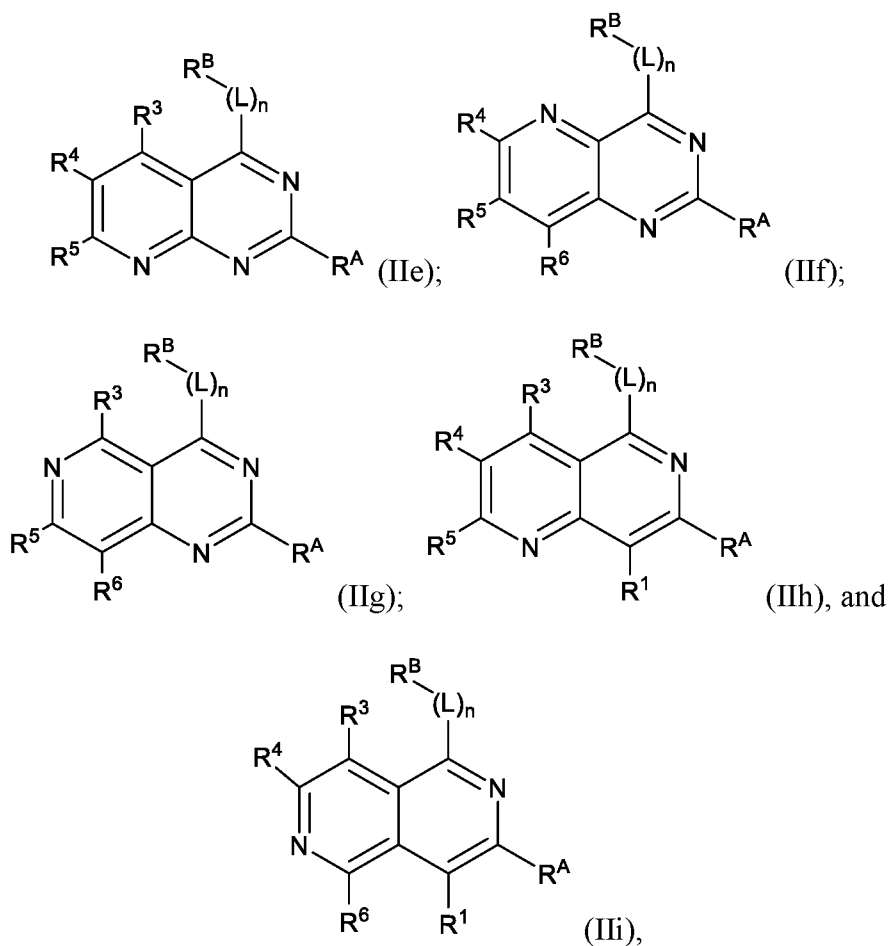
In some embodiments, this document provides a compound of Formula (IIb):



or a pharmaceutically acceptable salt thereof, wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^C , R^B , L , and n are as described herein.

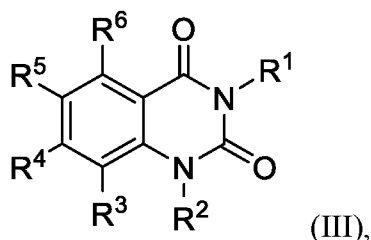
In some embodiments, this document provides a compound selected from any one of the following Formulae:





or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^A , R^B , L , and n are as described herein.

In some embodiments, this document provides a compound of Formula (III):



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as described herein.

In some embodiments, this document provides a pharmaceutical composition comprising any of the compounds described herein (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier.

In some embodiments, this document provides a method for increasing TFEB polypeptide levels within a cell and/or within the nucleus of a cell. The method comprises (or consists essentially of or consists of) administering, to a mammal (e.g.,

a human) containing the cell, a therapeutically effective amount of any one or more of the compounds described herein (or one or more pharmaceutically acceptable salts thereof).

In some embodiments, this document provides a method for treating a disease, disorder, or condition selected from the group consisting of lysosomal storage diseases (LSDs), acute or chronic inflammatory disorders, neurological diseases, conditions of age-related functional decline in a mammal (e.g., a human), and inherited or acquired diseases of muscle. The method comprises (or consists essentially of or consists of) administering, to a mammal (e.g., a human) having the disease, disorder, or condition, a therapeutically effective amount of any one or more of the compounds described herein (or one or more pharmaceutically acceptable salts thereof).

In some embodiments, this document provides a method for treating a disease, disorder, or condition selected from the group consisting of lysosomal storage diseases (LSDs), acute or chronic inflammatory disorders, neurological diseases, and conditions of age-related functional decline in a mammal (e.g., a human). The method comprises (or consists essentially of or consists of) administering, to a mammal (e.g., a human) having the disease, disorder, or condition, a therapeutically effective amount of any one or more of the compounds described herein (or one or more pharmaceutically acceptable salts thereof).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present application pertains. Methods and materials are described herein for use in the present application; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the present application will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1. Amino acid sequence of human TFEB polypeptide (SEQ ID NO:1).

FIGs. 2A-C. BC1753 increases TFEB polypeptide levels. A. The structure of BC1753 is provided. B. MLE12 cells stably expressing TFEB-EGFP were treated with the indicated amounts of BC1753 for 24 hours before immunoblotting for TFEB-GFP and β -actin. C. MLE12 cells stably expressing TFEB-EGFP were treated with the indicated amounts of BC1753 for 24 hours before imaging by confocal microscopy (scale bar = 10 μ m).

FIG. 3. High content screen assay (384 well) measuring TFEB nuclear accumulation. Approximately 2500 primary and immortalized human bronchial epithelial cells (BEAS-2B) stably expressing TFEB-EGFP in 25 μ L of HITEs media with 10% FBS were dispensed into 384 well plate (Black with glass bottom) and incubated for 8 hours. Compound serial dilution (DMEM low glucose media with 2% FBS, 25 μ L volume) were prepared using a robotic liquid handler. Compound solutions were then added to the cell plate and incubated for 18 hours. Cells were then fixed with 4% PFA followed by DAPI staining. TFEB localization was imaged on the GFP channel along with the DAPI signal using a Cytation 5 high content imager. Images were processed through Biotek Gen5 software; specifically, the DAPI signal was used as the primary mask to quantify the nuclear TFEB-GFP signal. The cytosolic TFEB-GFP signal was quantified through expanding the primary mask. The TFEB nuclear/cytosol ratios were calculated from nuclear TFEB-GFP signal/cytosol TFEB-GFP signal, which determined the compound efficacy. The table shows the efficacy of the compound (with increased compound concentrations) in increasing TFEB nuclear/cytosol ratio. Compound activities (μ M) were determined by the minimal compound concentration needed to increase TFEB nuclear/cytosol ratio by 25%. Activity: “-” equals $> 25 \mu$ M; “+” equals between $\leq 25 \mu$ M and $> 10 \mu$ M; “++” equals between $\leq 10 \mu$ M and $> 1 \mu$ M; and “+++” equals $\leq 1 \mu$ M. N=4.

FIGs. 4A-B. Compound 178 (BC1834) and Compound 160 (BC18200) increased lysosome quantity. A. Beas2B cells were treated with Cmpd. 178, Cmpd. 160, or the GSK3b inhibitor TWS119 (1 μ M for 18 hours). Cells were then imaged through light microscope. B. Beas2B cells were treated with Cmpd. 178 for 18 hours at the indicated concentrations. Cells were then stained with lysotracker Red (100

nM) for 30 minutes. Cells then were washed and imaged through confocal microscopy.

FIGs. 5A-B. Compound 133 and Compound 115 increased lysosomal protein expression and secretion. A. Beas2B cells were treated with Cmpd. 133 at 10 μ M for 24 hours. Cells then were collected and assayed for lysosomal protein gene expression. B. Beas2B cells were treated with Cmpd. 115 at the indicated concentration for 18 hours. Secreted b-hexosaminidase activity (a lysosomal enzyme) then was measured and normalized with cellular b-hexosaminidase activity.

FIGs. 6A-B. Compound 178 reduced Huntingtin gene expression. A-B. SH5Y cells stably transfected with GFP-72Q (Huntingtin) were treated with the indicated amounts of Cmpd. 178 for 24 hours. Cells then were imaged with a confocal microscope or collected and assayed for protein expression using a GFP-Huntingtin immunoblot.

FIG. 7. Compound 15 increases liver lysosomal activity. Female C57BL6 mice were intraperitoneally (i.p.) injected with Cmpd. 15 (50 mg/kg/d) for 4 days. Mice were then intravenously (i.v.) injected with dextran blue. 24 hours later, mice were sacrificed, and livers were removed and imaged through confocal microscopy. White fluorescent signal indicates dextran blue within lysosome and provides a measure of lysosomal number and activity within the hepatic tissue (Upper panels). In another experiment, histological slides from the liver obtained from the above experiment were immunostained with Lamp2 antibody (Lower panels) and revealed enhanced signals with Cmpd 15 treatment. Scale bar: 50 microns.

DETAILED DESCRIPTION

This document provides methods and materials for increasing TFEB polypeptide levels. For example, the document provides therapeutic compounds (e.g., therapeutic organic compounds) having the ability to increase TFEB polypeptide levels within cells, formulations containing therapeutic compounds having the ability to increase TFEB polypeptide levels within cells, methods for making therapeutic compounds having the ability to increase TFEB polypeptide levels within cells, methods for making formulations containing therapeutic compounds having the ability to increase TFEB polypeptide levels within cells, methods for increasing TFEB polypeptide levels within cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels. This

document also provides therapeutic compounds (e.g., organic compounds) having the ability to increase TFEB polypeptide levels within the nucleus of cells, formulations containing therapeutic compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for making therapeutic compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for making formulations containing therapeutic compounds having the ability to increase TFEB polypeptide levels within the nucleus of cells, methods for increasing TFEB polypeptide levels within the nucleus of cells, and methods for treating mammals (e.g., humans) having a condition responsive to an increase in TFEB polypeptide levels within the nucleus of cells.

Methods of treatment

The lysosome is the compartment within the cell which is responsible for the degradation of damaged proteins and organelles (e.g., mitochondria). Inside the lysosome, a very acidic pH is maintained, and there are a variety of digestive enzymes that can efficiently degrade organelles and various biomolecules such as proteins, lipids and nucleic acids, that are either damaged or no longer needed by the cell. Delivery of damaged contents to the lysosome can occur through multiple means, but one way the damaged cargo gets to the lysosome is through the process of macroautophagy ("autophagy" herein). In this case, the damaged biomolecules and organelles are wrapped within a double membrane structure known as the autophagosome that then fuses with the lysosome. This process is responsible for homeostatic maintenance of cells and tissues. In the absence of autophagic flux and functional lysosomes, damage biomolecules and organelles accumulate in the cell. These damaged and dysfunctional components can fuel a cycle of further damage. Breakdown of this system generally leads to a number of pathological conditions. In rare inherited conditions called lysosomal storage diseases (LSD), a child often has inherited two copies of a defective lysosomal enzyme. LSDs are a collection of roughly 50 different inherited conditions that render the patient's lysosomes incapable of metabolizing a specific molecule, which the missing enzyme normally degrades. This deficiency causes the undegraded molecules to build up within the lysosome and the lysosome to massively swell. As the lysosome enlarges and fills with undegraded material, it ultimately becomes dysfunctional not only for the degradation of the specific molecule typically digested by the missing enzyme, but for all of its recycling

capacity. Although recently a number of disease-specific replacement therapies have become available in which the child is given back the 'missing' enzyme to partially compensate for their inherited defect, in many lysosomal storage diseases no replacement therapy is currently available. Moreover, even when replacement therapies exist, these protein-based therapies are often only modestly successful as they often cannot treat conditions in the central nervous system (due to the blood-brain barrier) or gain entry to certain cell types. Besides LSDs, it is known that this process of autophagy and lysosomal degradation naturally slows with aging. The natural consequence is the age-dependent accumulation of damaged contents within cells and tissues. This can be harmful and can contribute to a range of age-dependent diseases. Augmenting autophagy and lysosomal function as described herein can be used to reverse this damage. In other conditions, stimulation of autophagy and lysosomal function can be beneficial. This includes metabolic conditions (e.g., non-alcoholic steatohepatitis (NASH) or fatty liver), neurodegenerative conditions (e.g., Parkinson's disease, ALS, Alzheimer's disease, and Huntington's disease), a range of other general age-related conditions (e.g., macular degeneration, sarcopenia, and frailty), non-neurological disorders of protein aggregation (e.g., α -1 antitrypsin, amyloidosis, and retinitis pigmentosa), or in conditions of impaired immunity (e.g., aiding the removal of microbiological pathogens including intracellular pathogens such as *Mycobacterium tuberculosis* or in conditions characterized by chronic bacterial colonization such as cystic fibrosis).

TFEB is a master regulator of lysosomal biogenesis. Increasing TFEB polypeptide levels within cells and/or within the nucleus of cells using a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) as described herein can result in one or more benefits for the cell and/or mammal. For example, increasing TFEB polypeptide levels within cells and/or within the nucleus of cells using a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) as described herein can result in increased lysosomal numbers within cells and/or increased lysosomal function within cells. In some cases, increasing TFEB polypeptide levels within cells and/or within the nucleus of cells using a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) as described herein can result in (a) an increased level of lysosomal exocytosis (the process of excreting the

contents of the lysosome out of the cell and into the serum), (b) transcriptionally augmenting multiple factors that regulate autophagy, and/or (c) a coordinated increase in intracellular recycling capacity and the removal of intracellular debris (e.g., increasing autophagy, lysosomal numbers, and lysosomal exocytosis). In some cases, increasing TFEB polypeptide levels within cells and/or within the nucleus of cells using a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) as described herein can result in reducing one or more symptoms associated with a LSD, an α -1 antitrypsin deficiency, a neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease, ALS, or Huntington's disease), a metabolic disease (e.g., NASH), or an age-related condition (e.g., sarcopenia).

In some cases, this document provides methods for increasing TFEB polypeptide levels within cells and/or within the nucleus of cells by contacting the cell with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof). The increase in TFEB polypeptide levels can be as compared to the TFEB polypeptide levels prior to the contacting step. In some cases, methods for increasing TFEB polypeptide levels within cells and/or within the nucleus of cells can be performed *in vivo*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) can be administered to a mammal (e.g., a human) to increase TFEB polypeptide levels within cells and/or within the nucleus of cells within that mammal. In some cases, methods for increasing TFEB polypeptide levels within cells and/or within the nucleus of cells can be performed *in vitro*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) can be added to a cell culture containing cells (e.g., human cells) to increase TFEB polypeptide levels within those cells and/or within the nucleus of those cells. In some cases, such intervention can improve the quality of the cell while in culture or subsequently. In some cases, one or more of the compounds provided herein can be used during an *ex vivo* expansion of a genetically engineered T cell (e.g., CAR T cell) or tumor-infiltrating T cell (e.g., TIL) so that the treated T cells exhibit improved *in vivo* persistence and/or efficacy. A range of other cellular products that are to be ultimately infused into a mammal (e.g., a human) can be treated as described herein during their *in vitro* expansion.

In some cases, this document provides methods for increasing lysosomal exocytosis in a cell by contacting the cell with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof). The increase in lysosomal exocytosis can be as compared to the lysosomal exocytosis levels prior to the contacting step. In some cases, methods for increasing lysosomal exocytosis in a cell can be performed *in vivo*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be administered to a mammal (e.g., a human) to increase lysosomal exocytosis in a cell within that mammal. In some cases involving a LSD, one or more compounds provided herein can be administered to a mammal having a LSD so that undegraded lysosomal material that accumulated is released via exocytosis from the diseased cell, tissue, and/or organ. In some cases, methods for increasing lysosomal exocytosis in a cell can be performed *in vitro*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be added to a cell culture containing cells (e.g., human cells) to increase lysosomal exocytosis in those cells.

In some cases, this document provides methods for increasing cellular autophagy in a cell by contacting the cell with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof). The increase in cellular autophagy can be as compared to the cellular autophagy levels prior to the contacting step. In some cases, methods for increasing cellular autophagy in a cell can be performed *in vivo*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be administered to a mammal (e.g., a human) to increase cellular autophagy in a cell within that mammal. In some cases, methods for increasing cellular autophagy in a cell can be performed *in vitro*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be added to a cell culture containing cells (e.g., human cells) to increase cellular autophagy in those cells.

In some cases, this document provides methods for increasing nuclear localization of TFEB polypeptides in a cell by contacting the cell with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or

(III), or a pharmaceutically acceptable salt thereof). The increase in nuclear localization of TFEB polypeptides can be as compared to the level of nuclear localization of TFEB polypeptides prior to the contacting step. In some cases, methods for increasing nuclear localization of TFEB polypeptides in a cell can be performed *in vivo*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be administered to a mammal (e.g., a human) to increase nuclear localization of TFEB polypeptides in a cell within that mammal. In some cases, methods for increasing nuclear localization of TFEB polypeptides in a cell can be performed *in vitro*. For example, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be added to a cell culture containing cells (e.g., human cells) to increase nuclear localization of TFEB polypeptides in those cells.

This document also provides methods for treating diseases, disorders, and conditions in a mammal by administering one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) to a mammal in need thereof. In some cases, the disease, disorder, or condition being treated can be a disease, disorder, or condition that is responsive to an increase in TFEB polypeptide levels within cells and/or within the nucleus of cells within the mammal. In some cases, the disease, disorder, or condition being treated can be a disease, disorder, or condition that is associated with low TFEB polypeptide levels within cells and/or within the nucleus of cells within the mammal. Examples of diseases, disorders, and conditions that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) as described herein include, without limitation, lysosomal storage diseases, acute or chronic inflammation disorders, conditions associated with age-related functional decline, acute or chronic organ failure (e.g., kidney, lung, cardiac, or hepatic organ dysfunction), disorders of protein aggregation, neurodegenerative conditions, and inherited or acquired diseases of muscle. Examples of diseases, disorders, and conditions that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) as described herein include, without limitation, lysosomal storage diseases, acute or chronic inflammation disorders, conditions associated with age-related functional decline, acute or chronic

organ failure (e.g., kidney, lung, cardiac, or hepatic organ dysfunction), disorders of protein aggregation, and neurodegenerative conditions.

Examples of lysosomal storage diseases that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) as described herein include, without limitation, Krabbe disease, Sanfilippo syndrome, multiple sulfatase deficiency, alpha-mannosidosis, Fabry disease, Hunter syndrome, Scheie syndrome, Sanfilippo syndrome, Maroteaux–Lamy syndrome, hyaluronidase deficiency, Sialidosis, mucopolipidin 1 deficiency, Neuronal ceroid lipofuscinoses (Batten Disease), Mucopolysaccharidoses Type I, II, III, IV, VI, VII, and IX, Hurler–Scheie syndrome, Morquio syndrome, Glycoproteinosis, Glycogen storage disease, Metachromatic Leukodystrophy, Sly syndrome, I-cell disease, Danon disease, Niemann-Pick disease Type A, B, C1, and C2, Sandhoff disease, Lysosomal acid lipase deficiency, GM2 gangliosidoses, Tay–Sachs disease, Gaucher disease, Salla disease, Pompe disease, Danon disease, cholesteryl ester storage disease, Aspartylglucosaminuria, Cystinosis, Mucopolipidosis Type I-IV, Schindler Disease Type I and II, Wolman disease, Fucosidosis, Pycnodysostosis, and Free Sialic Acid Storage Disease.

Examples of acute or chronic inflammation disorders that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) as described herein include, without limitation, asthma, chronic obstructive lung disease, pulmonary fibrosis, pneumonitis (e.g., hypersensitivity pneumonitis or radiation pneumonitis), pneumonia, cystic fibrosis, psoriasis, arthritis/rheumatoid arthritis, rhinitis, pharyngitis, cystitis, prostatitis, dermatitis, allergy including hayfever, nephritis, conjunctivitis, encephalitis, meningitis, ophthalmitis, uveitis, pleuritis, pericarditis, myocarditis, atherosclerosis, human immunodeficiency virus related inflammation, diabetes, osteoarthritis, psoriatic arthritis, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), colitis, sepsis, vasculitis, bursitis, connective tissue disease, autoimmune diseases (e.g., systemic lupus erythematosus (SLE)), polymyalgia rheumatica, scleroderma, Wegener's granulomatosis, temporal arteritis, vasculitis, cryoglobulinemia, multiple sclerosis, viral or influenza-induced inflammation, chronic bacterial colonization or persistent intracellular pathogen, and impaired responsiveness to antigenic challenge or vaccines administration.

Examples of conditions associated with age-related functional decline that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) as described herein include, without limitation, neurodegenerative diseases (e.g., Alzheimer's, ALS, Huntington's disease, Parkinson's disease, primary age-related tauopathy, progressive supranuclear palsy, chronic traumatic encephalopathy, acute or chronic traumatic brain injury, and frontotemporal dementia), metabolic diseases (e.g., NASH), metabolic syndrome, diabetes, sarcopenia, frailty, macular degeneration, other inherited or acquired retinal degenerative diseases, age-related hearing loss, early cognitive decline, osteoporosis, acute or age-related organ dysfunction (e.g., heart and/or kidney dysfunction), age-related immune dysfunction (e.g., impaired response to vaccination or immunosenescence), and other non-neurological disorders of protein aggregations (e.g., amyloidosis or α -1 antitrypsin deficiency).

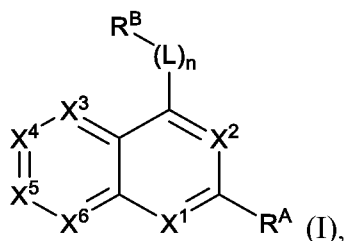
Examples of inherited or acquired diseases of muscle that can be treated with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) include, without limitation, myofibrillar myopathy, sporadic inclusion body myositis, inclusion body myopathy with frontotemporal dementia (IBMFTD), and cardiomyopathy (e.g., dilated cardiomyopathy, or proteotoxic cardiomyopathy such as advanced proteotoxic cardiomyopathy).

In some cases, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be used as described herein (e.g., to increase TFEB polypeptide levels within the nucleus of cells and/or to treat a disease, disorder, or condition as described herein) as the sole active ingredient(s). For example, a composition containing a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof can lack any other active ingredients that increase TFEB polypeptide levels within the nucleus of cells. In some cases, a composition containing a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof can lack any other active ingredients that are effective to treat a disease, disorder, or condition as described herein.

Therapeutic compounds

As described herein, any one or more of the compounds provided herein can be used to increase TFEB polypeptide levels within cells and/or within the nucleus of cells, to increase lysosomal exocytosis in a cell, to increase cellular autophagy in a cell, to increase nuclear localization of TFEB polypeptides in a cell, and/or to treat a disease, disorder, and condition described herein in a mammal.

In some embodiments, this document provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from O, S, S(=O)₂, C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

each R^N is independently selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

n is an integer selected from 1, 2, and 3;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

X³ is selected from N, N⁺-O⁻, and CR³;

X⁴ is selected from N, N⁺-O⁻, and CR⁴;

X⁵ is selected from N, N⁺-O⁻, and CR⁵;

X⁶ is selected from N, N⁺-O⁻, and CR⁶;

provided that no more than four of X¹, X², X³, X⁴, X⁵, and X⁶ are N;

each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from

CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},
NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and N(R^N)-Cy^{A1};

Cy^{A1} is selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and
4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3,
4, or 5 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and Cy¹,
wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted
with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{a1},
C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1},
NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to L which is N(R^N), R^B and R^N together with the N atom
to which they are attached form 4-14 membered heterocycloalkyl, which is optionally
substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN,

NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a1}, C(O)R^{b1},
C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1},
S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl
are each optionally substituted with 1, 2, or 3 substituents independently selected from
Cy¹, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},
NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₄ cycloalkyl, 5-10
membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is
optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from
R^{Cy2};

R^{Cy1} and R^{Cy2} are each independently selected from oxo, halo, CN, NO₂, Cy², C₁₋₆
alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2},
C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and
S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each
optionally substituted with 1, 2, or 3 substituents independently selected from Cy²,
halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2},
NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each Cy² is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10
membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is
optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments:

R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, and

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} .

In some embodiments:

R^A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} ; and

R^{Cy1} and R^{Cy2} are each independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

In some embodiments, L is independently selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH.

In some embodiments, L is C_{1-3} alkylene, which is optionally substituted with halo, CN, NO_2 , OH, C_{1-3} alkoxy, or amino.

In some embodiments, L is C_{1-3} alkylene, which is optionally substituted with OH.

In some embodiments, L is $C(=O)$.

In some embodiments, L is $N(R^N)$.

In some embodiments, R^N is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2 , and C_{1-3} alkoxy.

5 In some embodiments, R^N is selected from H and C_{1-6} alkyl. In some embodiments, R^N is H. In some embodiments, R^N is C_{1-6} alkyl, optionally substituted with halo, CN, NO_2 , or C_{1-3} alkoxy.

In some embodiments, L is NH.

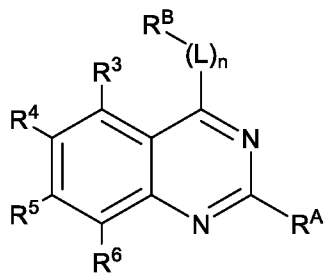
10 In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, OR^{a1} , $NR^{c1}R^{d1}$, and $S(O)_2R^{b1}$.

15 In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, the compound of Formula (I) has formula:

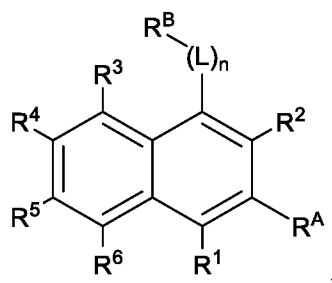


20

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, R^3 , R^4 , R^5 , and R^6 are each H.

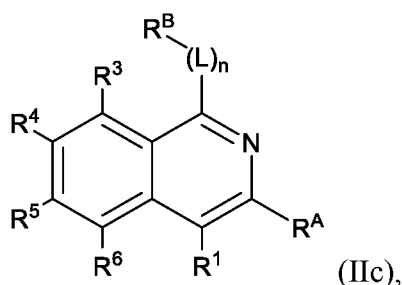
In some embodiments, the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently
 5 selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is H.

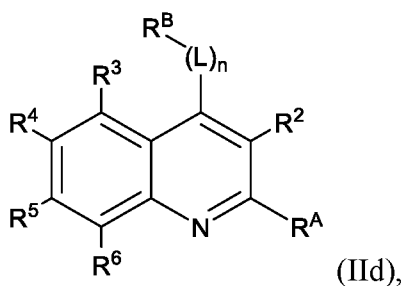
In some embodiments, the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

10 In some embodiments, R^1 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, R^1 , R^3 , R^4 , R^5 , and R^6 are each H.

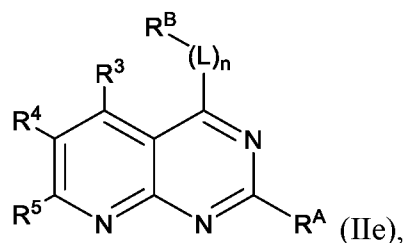
In some embodiments, the compound of Formula (I) has formula:



15 or a pharmaceutically acceptable salt thereof.

In some embodiments, R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, R^2 , R^3 , R^4 , R^5 , and R^6 are each H.

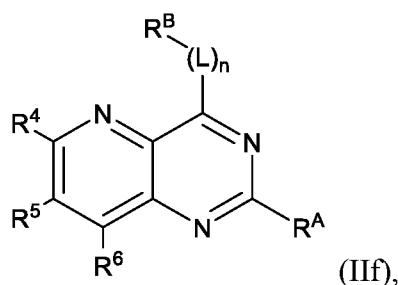
In some embodiments, the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R³, R⁴, and R⁵ are each independently selected from H,
 5 halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy. In some embodiments, R³, R⁴, and R⁵ are each H.

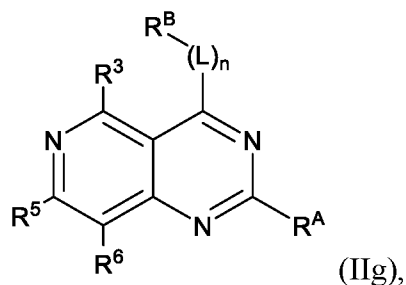
In some embodiments, the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R⁴, R⁵, and R⁶ are each independently selected from H,
 10 halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy. In some embodiments, R⁴, R⁵, and R⁶ are each H.

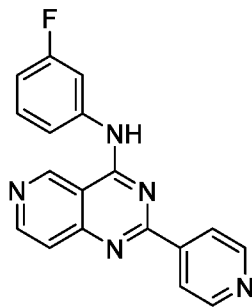
In some embodiments, the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R³, R⁵, and R⁶ are each independently selected from H,
 15 halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy. In some embodiments, R³, R⁵, and R⁶ are each H.

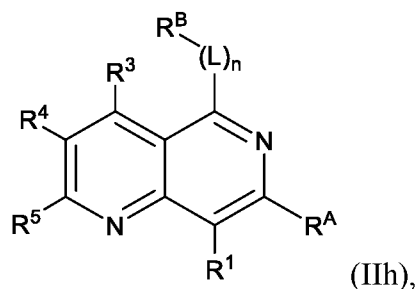
In some embodiments of the compound of Formula (IIg), the compound of Formula (IIg) is not:



In some embodiments, of the compound of Formula (IIg), R^B is selected from 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, of the compound of Formula (IIg), R^B is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} . In some embodiments of Formula (IIg), R^B is not C₆₋₁₀ aryl substituted with one halo.

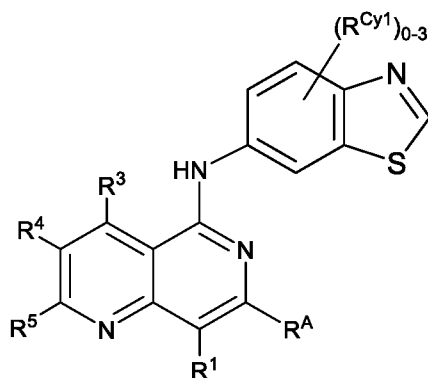
In some embodiments, the compound of Formula (I) has formula (IIh):



or a pharmaceutically acceptable salt thereof.

In some embodiments, of the compound of Formula (IIh), R^B is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, the compound of Formula (IIh) has formula:

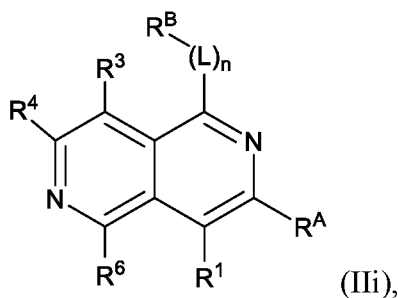


or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (IIh), each of R¹, R³, R⁴, and R⁵ is independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1}.

In some embodiments of Formula (IIh), R³ is selected from H, halo, CN, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1}. In some embodiments of Formula (IIh), R¹ is selected from H, halo, and C₁₋₆ alkyl.

In some embodiments, the compound of Formula (I) has formula (IIi):



or a pharmaceutically acceptable salt thereof.

In some embodiments, of the compound of Formula (IIi), R^B is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2}. In some embodiments, of the compound of Formula (IIi), R^A is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}. In some embodiments, of the compound of Formula (IIi), R¹, R³, R⁴, and R⁶ are each H.

In some embodiments, the present disclosure provides a compound selected from any one of the following Formulae (IIc)-(IIi), or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound selected from any one of the following Formulae (IIc)-(IIg), or a pharmaceutically acceptable salt thereof.

In some embodiments, R^A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} .

5 In some embodiments, R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .

In some embodiments, R^A is Cy^{A1} .

In some embodiments, R^A is $O-Cy^{A1}$.

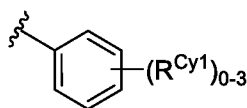
10 In some embodiments, R^A is $NH-Cy^{A1}$.

In some embodiments, Cy^{A1} is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} .

15 In some embodiments, Cy^{A1} is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} .

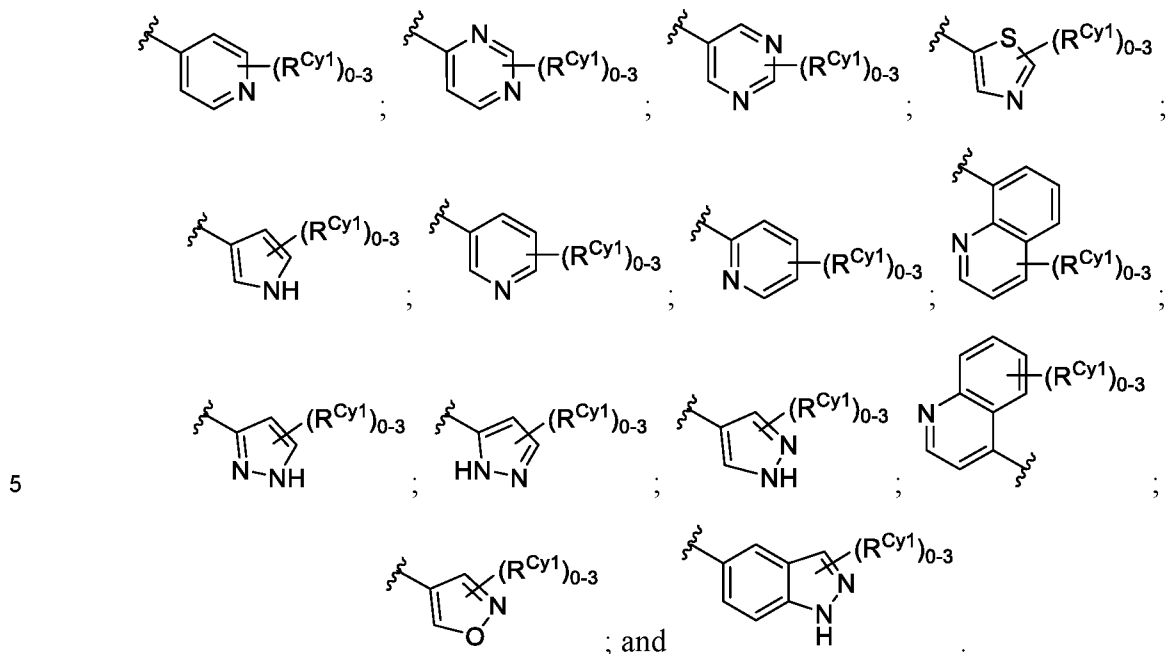
In some embodiments, Cy^{A1} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .

20 In some embodiments, Cy^{A1} is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} . In some embodiments, the C_{6-10} aryl has the formula:

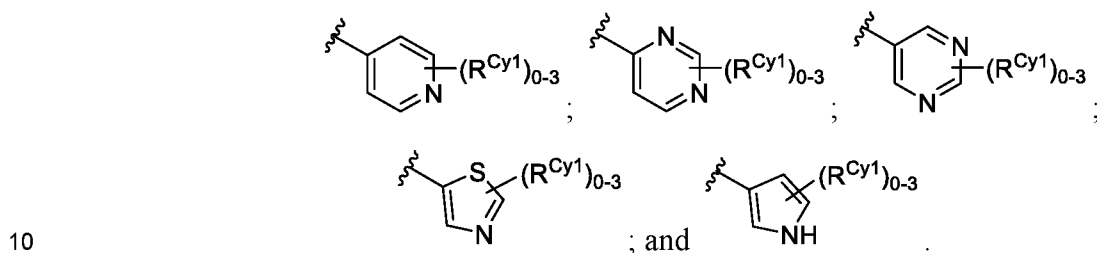


25 In some embodiments, Cy^{A1} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .

In some embodiments, the 5-10 membered heteroaryl has the formula selected from:

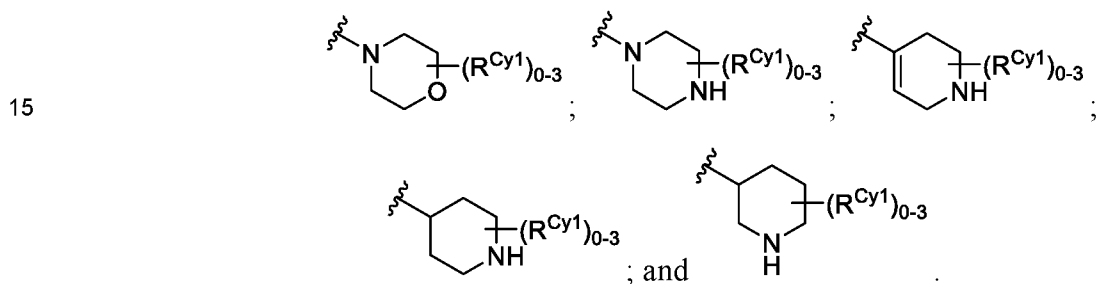


In some embodiments, the 5-10 membered heteroaryl has the formula selected from:

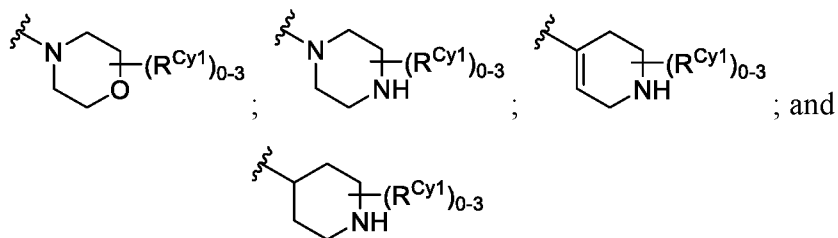


In some embodiments, Cy^{A1} is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

In some embodiments, the 4-10 membered heterocycloalkyl has the formula selected from:



In some embodiments, the 4-10 membered heterocycloalkyl has the formula selected from:



5 In some embodiments, each R^{Cy1} is independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from
10 Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} .

15 In some embodiments, each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$.

In some embodiments, each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OH, C_{1-6} alkoxy, and $C(O)(C_{1-6} \text{ alkoxy})$.

20 In some embodiments, each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} alkoxy, and $C(O)(C_{1-6} \text{ alkoxy})$.

In some embodiments, R^{Cy1} is selected from Cl and F. In some embodiments, R^{Cy1} is NO_2 . In some embodiments, R^{Cy1} is C_{1-6} alkyl or C_{1-6} alkoxy.

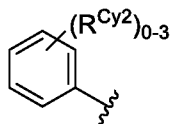
In some embodiments, R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected
25 from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, R^B is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

30 In some embodiments, R^B is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OH, $S(O)_2CH_3$, and $S(O)_2NH_2$.

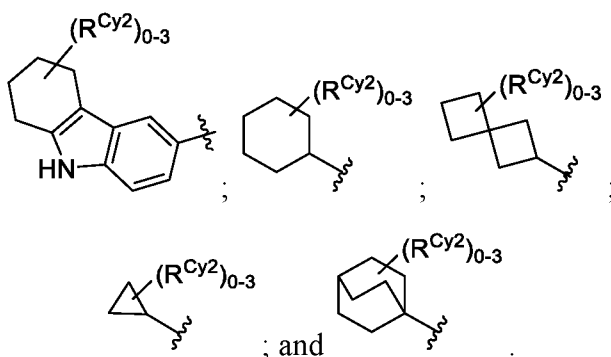
In some embodiments, R^B is Cy^1 .

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} . In some embodiments, the C_{6-10} aryl has formula:



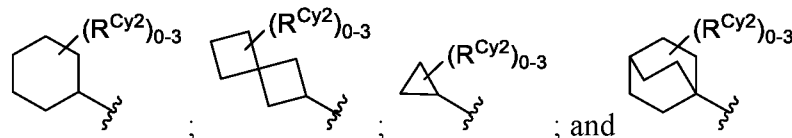
5 In some embodiments, Cy^1 is C_{3-14} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, Cy^1 is C_{3-14} cycloalkyl having the formula selected from:



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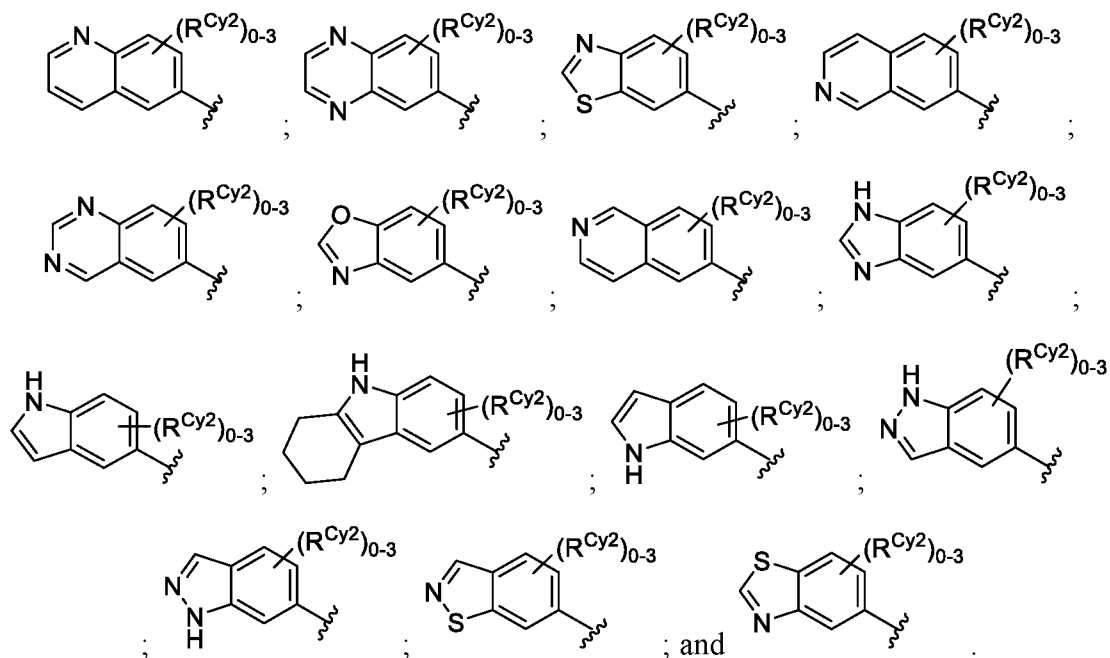
In some embodiments, Cy^1 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} . In some embodiments, the C_{3-10} cycloalkyl has the formula selected from:



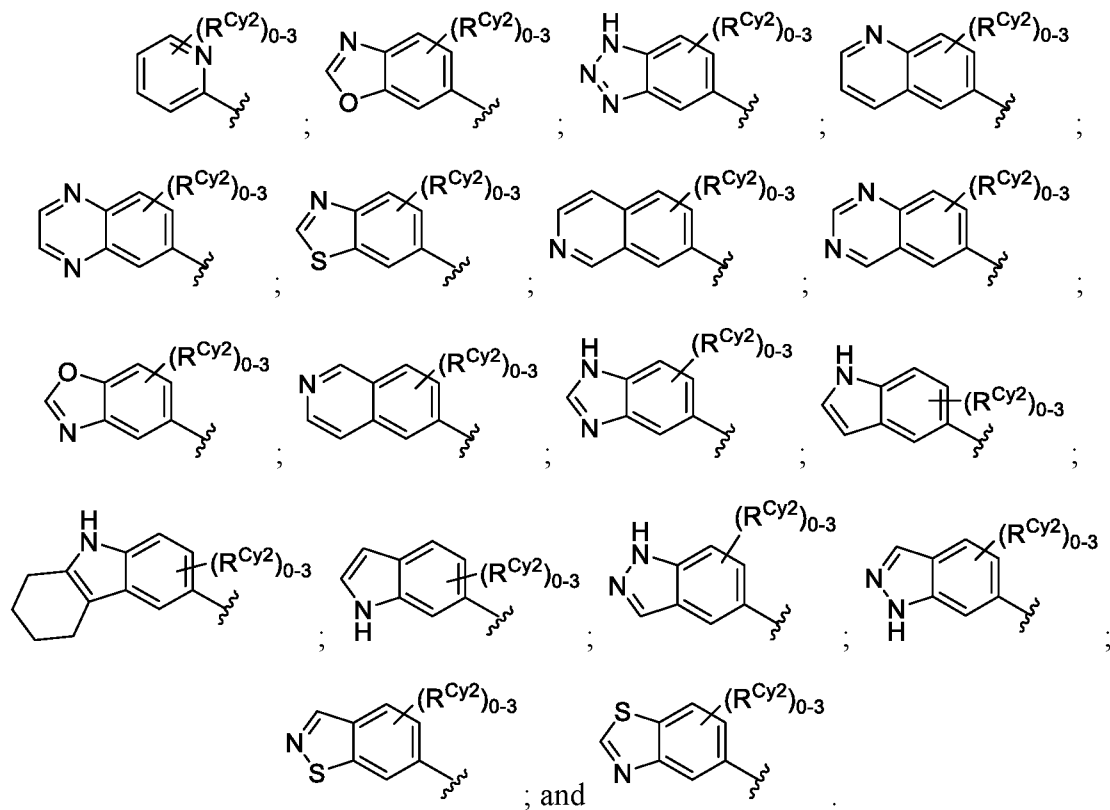
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In some embodiments, Cy^1 is 4-14 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, Cy^1 is 4-14 membered heterocycloalkyl having the formula selected from:



5 In some embodiments, the 5-10 membered heteroaryl has the formula selected from:



10

In some embodiments, wherein each R^{Cy2} is independently selected from halo, CN, NO₂, Cy², C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl

15

are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , $\text{OR}^{\text{a}2}$, $\text{C(O)R}^{\text{b}2}$, $\text{C(O)NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{C(O)OR}^{\text{a}2}$, $\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{C(O)R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{C(O)OR}^{\text{a}2}$, $\text{NR}^{\text{c}2}\text{S(O)}_2\text{R}^{\text{b}2}$, $\text{S(O)}_2\text{R}^{\text{b}2}$, and $\text{S(O)}_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$.

In some embodiments, each $\text{R}^{\text{Cy}2}$ is independently selected from halo, Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, $\text{OR}^{\text{a}2}$, $\text{C(O)NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{C(O)R}^{\text{b}2}$, and $\text{S(O)}_2\text{R}^{\text{b}2}$.

In some embodiments, each $\text{R}^{\text{Cy}2}$ is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $\text{OR}^{\text{a}2}$, $\text{C(O)R}^{\text{b}2}$, $\text{C(O)NR}^{\text{c}2}\text{R}^{\text{d}2}$, and $\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$.

In some embodiments, each $\text{R}^{\text{Cy}2}$ is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $\text{C(O)(C}_{1-6}\text{ alkyl)}$, C(O)NH_2 , and NH_2 .

In some embodiments, $\text{R}^{\text{Cy}2}$ is halo.

In some embodiments, $\text{R}^{\text{Cy}2}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy.

In some embodiments, $\text{R}^{\text{Cy}2}$ is NH_2 .

In some embodiments, each $\text{R}^{\text{a}1}$, $\text{R}^{\text{b}1}$, $\text{R}^{\text{c}1}$, $\text{R}^{\text{d}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{b}2}$, $\text{R}^{\text{c}2}$, and $\text{R}^{\text{d}2}$ is independently selected from H and C_{1-6} alkyl.

In some embodiments, R^{B} is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}2}$; and R^{A} is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}1}$.

In some embodiments, R^{B} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}2}$; and R^{A} is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}1}$.

In some embodiments, R^{B} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}2}$; and R^{A} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}1}$.

In some embodiments, R^{B} is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}2}$; and R^{A} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from $\text{R}^{\text{Cy}1}$.

In some embodiments:

n is 1;

L is selected from C_{1-3} alkylene, C(=O) , and $\text{N(R}^{\text{N}})$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^{N} is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and NH-Cy^{A1};

each Cy^{A1} is selected from C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, OR^{a1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to N(R^N), R^B and R^N together with the N atom to which they are attached form 4-14 membered heterocycloalkyl, which is optionally substituted with Cy¹, C₁₋₆ alkyl, OR^{a1}, and halo;

each R^{Cy1} is independently selected from halo, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, and S(O)₂R^{b2}, wherein said C₁₋₆ alkyl is optionally substituted with OR^{a2};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₄ cycloalkyl, 5-10 membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2};

each R^{Cy2} is independently selected from halo, Cy², C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, and S(O)₂R^{b2}; and

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H and C₁₋₆ alkyl.

In some embodiments:

n is 1;

L is selected from C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with OH;

R^N is selected from H and C₁₋₆ alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and NH-Cy^{A1};

each Cy^{A1} is selected from C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} ;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

n is 1;

L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^N is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and OR^{a1} ;

R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 1a, Table 2, Table 3, Table 5, Table 5a, and Table 6, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 1a, Table 2, Table 3, Table 5, and Table 6, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 2, or Table 3, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 1a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 3, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 5, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 5a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is selected from any one of the compounds in Table 6, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of Formulae (IIc)-(IIIi).

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:

BC18618	
BC18664	
BC18666	
BC18670	
BC18702	
BC18703	

BC18704	
BC18705	
BC18706	
BC18720	
BC18722	
BC18738	

BC18740	
BC18742	
BC18853	
BC18854	
BC191107	
BC191108	

BC191109	
BC191110	
BC191111	
BC191112	
BC191113	
BC191114	

BC191115	
BC191116	
BC191117	
BC191118	
BC191119	

BC191120	
BC191121	
BC191122	
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BC191127	
BC191128	
BC191129	
BC191130	
BC191131	

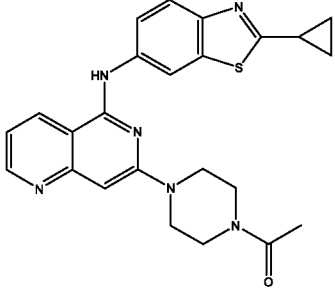
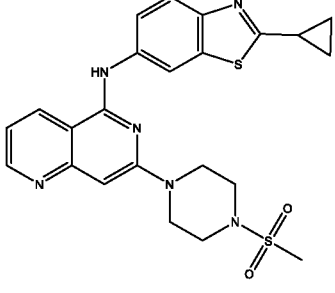
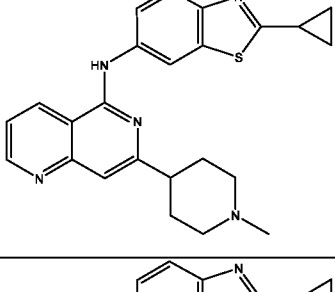
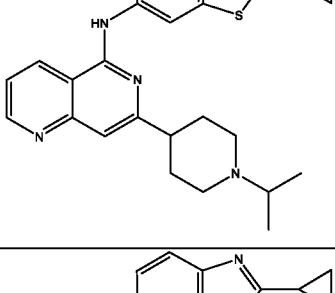
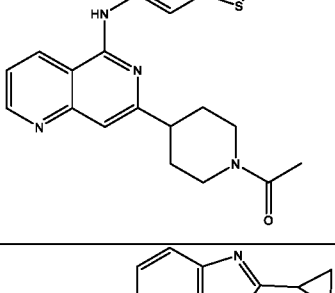
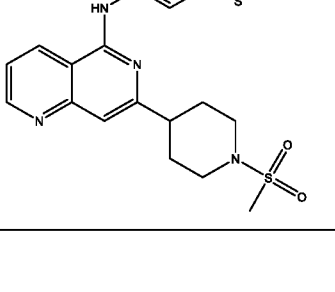
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BC191133	
BC191134	
BC191135	
BC191136	
BC191137	

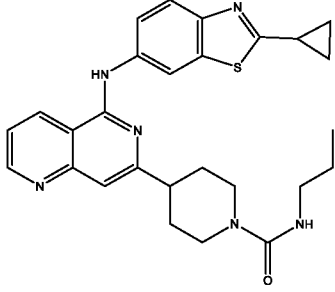
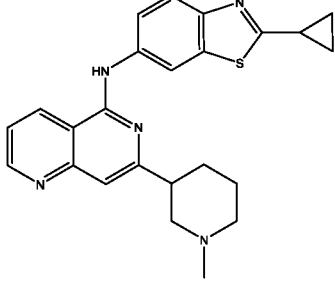
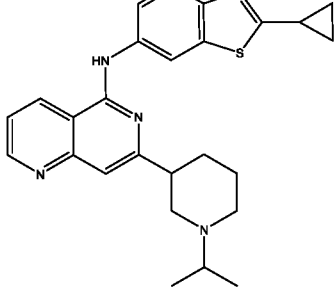
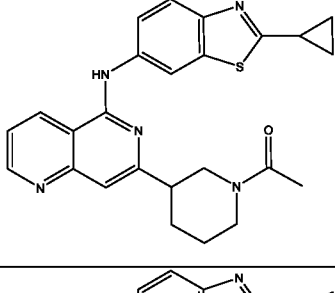
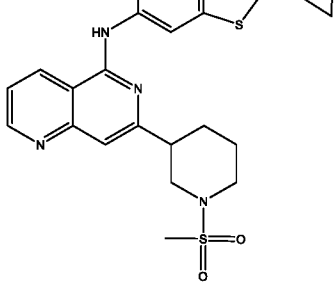
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BC191140	
BC191142	
BC191143	
BC191144	

BC191145	
BC191146	
BC191147	
BC191148	
BC191149	

BC191150	
BC191151	
BC191152	
BC191155	
BC191156	

BC191157	
BC191158	
BC191159	
BC191160	
BC191161	

BC191162	
BC191163	
BC191164	
BC191165	
BC191166	
BC191167	

BC191168	
BC191169	
BC191170	
BC191171	
BC191172	

BC191173	
BC191185	
BC191186	
BC191187	
BC191188	
BC191189	

BC191190	
BC191191	
BC191192	
BC191193	
BC191194	
BC191195	

BC191196	
BC191197	
BC191198	
BC191199	
BC191200	
BC191201	

BC191202	
BC18829	
BC18830	
BC18831	
BC18832	
BC18833	
BC18834	

BC18835	
BC18836	
BC18838	
BC18839	

BC18840	
BC18841	
BC18845	

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:

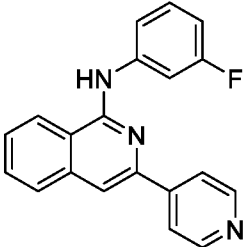
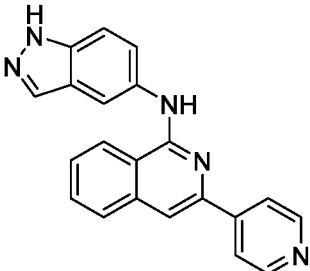
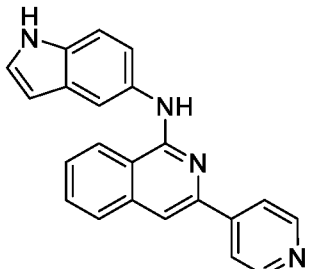
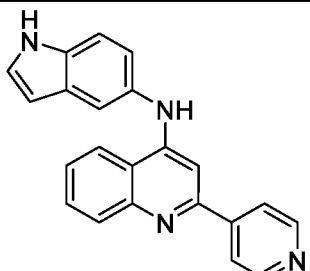
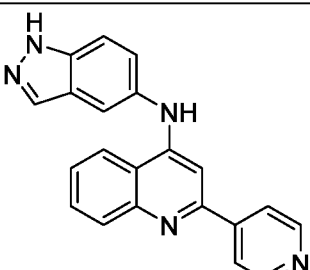
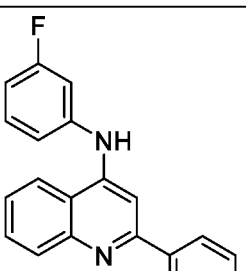
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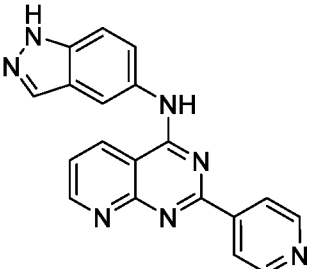
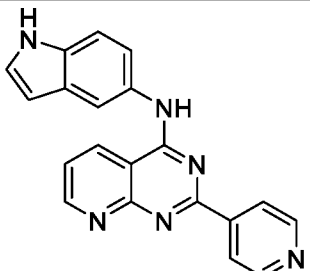
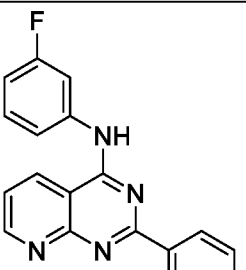
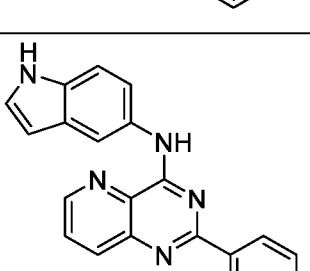
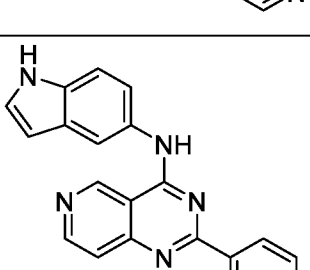
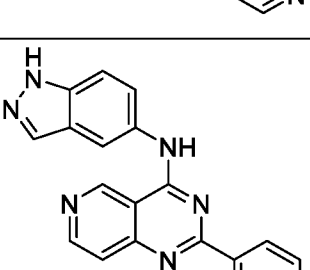
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BC18670	

BC18702	
BC18703	
BC18704	
BC18705	
BC18706	
BC18720	
BC18722	
BC18738	
BC18740	
BC18742	

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of any one of Formulae (IIc)-(IIi) is selected from any one of the following compounds:

BC18663	
BC18668	
BC18669	
BC18687	
BC18688	
BC18689	

BC18707	
BC18708	
BC18709	
BC18711	
BC18713	
BC18714	

BC18755	
BC18756	
BC18757	
BC18758	
BC18759	
BC18760	

BC18761	
BC18762	
BC18763	
BC18764	
BC18765	
BC18766	

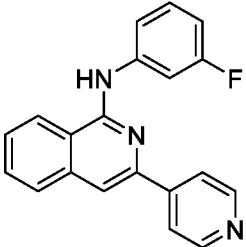
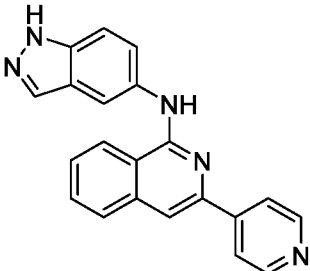
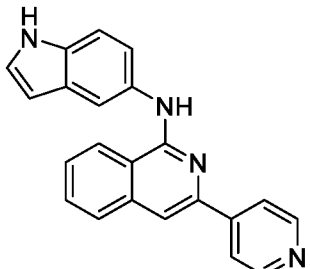
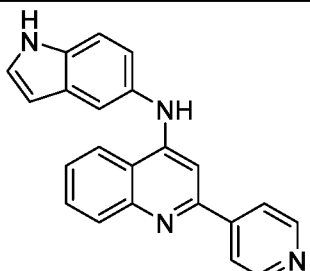
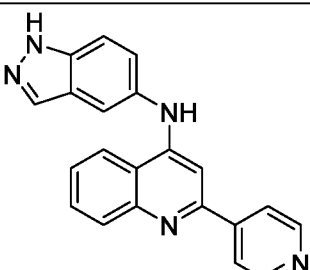
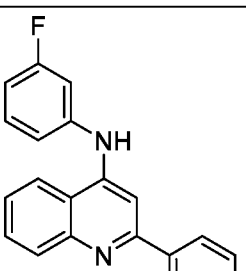
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BC18772	

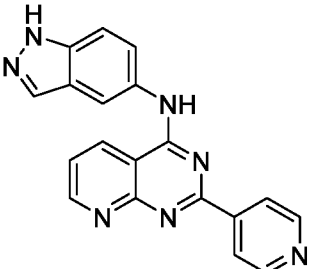
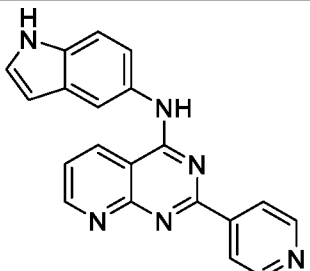
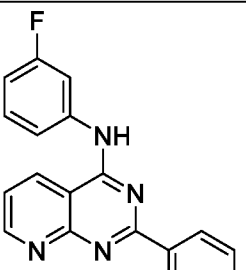
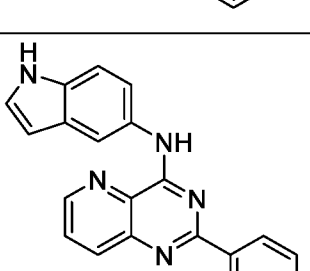
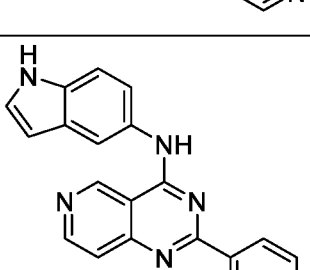
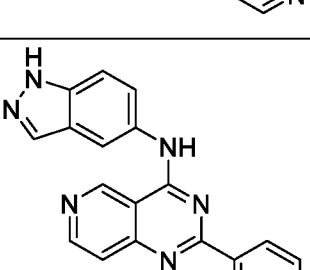
BC18773	
BC18774	
BC18775	
BC18776	
BC18778	
BC18783	

BC18785		BC18829	
BC18796		BC18830	
BC18799		BC18831	
BC18801		BC18832	
BC18806		BC18837	
BC18808		BC18845	
BC18821			

or a pharmaceutically acceptable salt thereof.

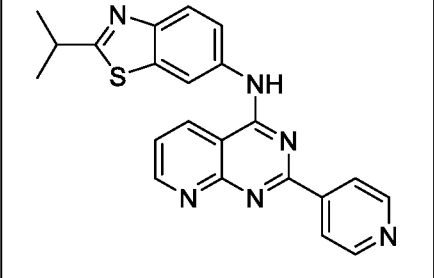
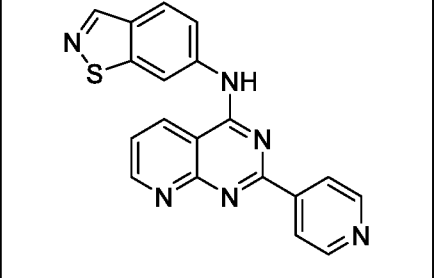
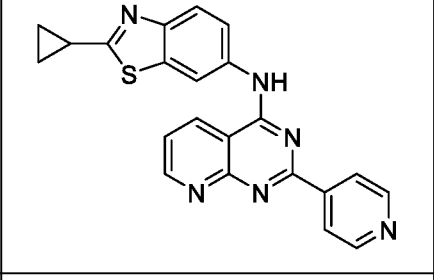
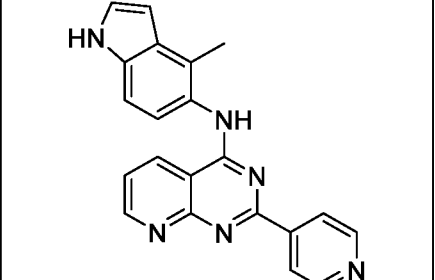
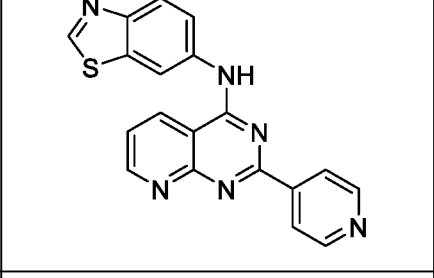
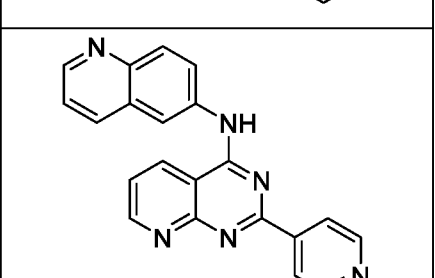
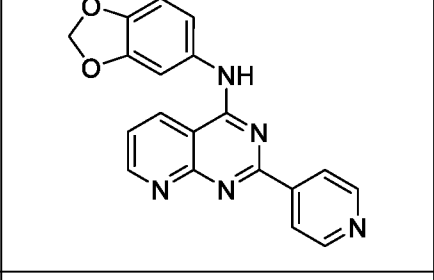
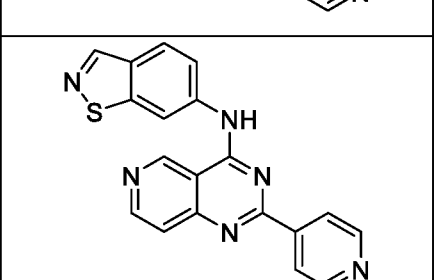
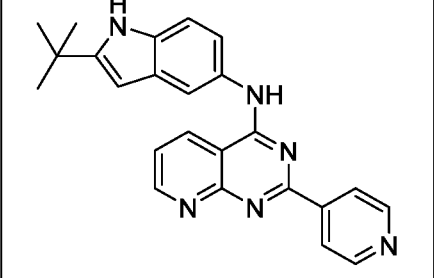
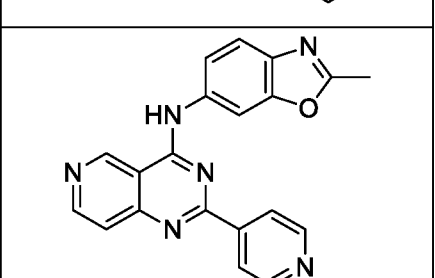
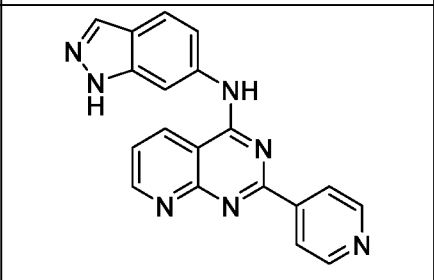
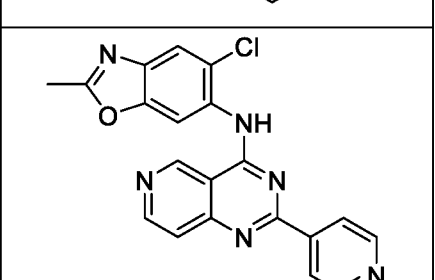
In some embodiments, the compound of any one of Formulae (IIc)-(Ili) is selected from any one of the following compounds:

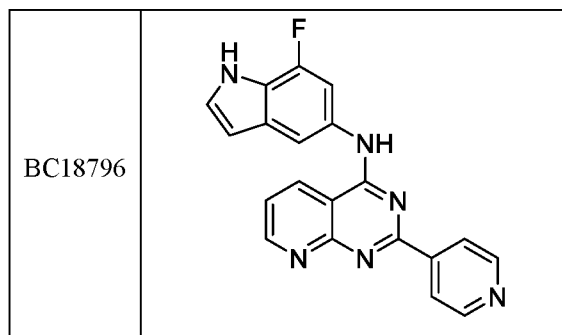
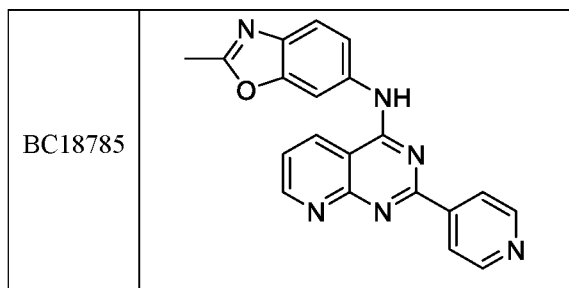
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BC18689	

BC18707	
BC18708	
BC18709	
BC18711	
BC18713	
BC18714	

BC18755	
BC18756	
BC18757	
BC18758	
BC18759	
BC18760	

BC18761	
BC18762	
BC18763	
BC18764	
BC18765	
BC18766	

BC18767		BC18773	
BC18768		BC18774	
BC18769		BC18775	
BC18770		BC18776	
BC18771		BC18778	
BC18772		BC18783	



or a pharmaceutically acceptable salt thereof.

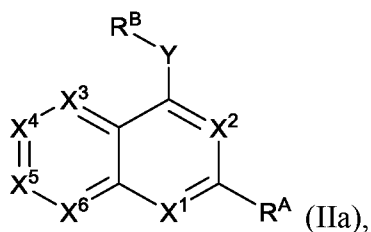
In some embodiments, the compound of Formula (IIh) is selected from any one of the compounds listed in Table 5, or a pharmaceutically acceptable salt thereof.

5 In some embodiments, the compound of Formula (IIh) is selected from any one of the compounds listed in Table 5a, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIh) is selected from any one of the compounds listed in Table 5 or Table 5a, or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the compound of Formula (IIi) is selected from any one of the compounds listed in Table 6, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) has Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein:

15 Y is selected from C(=O) and C(R⁷)(R⁸);

R⁷ and R⁸ are each independently selected from H, halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

20 X³ is selected from N, N⁺-O⁻, and CR³;

X⁴ is selected from N, N⁺-O⁻, and CR⁴;

X⁵ is selected from N, N⁺-O⁻, and CR⁵;

X⁶ is selected from N, N⁺-O⁻, and CR⁶;

provided that no more than four of X¹, X², X³, X⁴, X⁵, and X⁶ are N;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^A is selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and Cy¹, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2};

each R^{Cy1} and R^{Cy2} is independently selected from halo, CN, NO₂, Cy², C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy², halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each Cy² is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from

halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

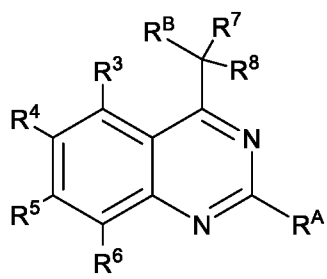
each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments, the compound of Formula (IIa) has formula:



or a pharmaceutically acceptable salt thereof.

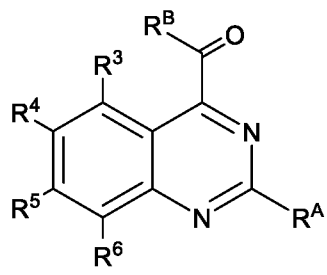
In some embodiments, R^7 is H, and R^8 is selected from H, halo, CN, NO₂, OH,
5 and C₁₋₃ alkoxy. In some embodiments, R^7 is H and R^8 is selected from H and OH.

In some embodiments, Y is CH₂.

In some embodiments, Y is CH(OH).

In some embodiments, Y is C(=O).

In some embodiments, the compound of Formula (IIa) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (IIa), R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each
independently selected from H, halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy. In some
embodiments, R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C₁₋₆
15 alkyl, and C₁₋₆ alkoxy. In some embodiments, R^3 , R^4 , R^5 , and R^6 are each H.

In some embodiments of Formula (IIa), R^B is selected from C₆₋₁₀ aryl, C₃₋₁₀
cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of
which is optionally substituted with 1, 2, or 3 substituents independently selected
from R^{Cy2}.

20 In some embodiments of Formula (IIa), R^B is C₆₋₁₀ aryl, optionally substituted
with halo.

In some embodiments of Formula (IIa), R^A is selected from C₆₋₁₀ aryl, 5-10
membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is
optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

In some embodiments of Formula (IIa), R^A is 5-10 membered heteroaryl, optionally substituted with halo, NO_2 , C_{1-6} alkyl, or C_{1-6} alkoxy.

In some embodiments of Formula (IIa):

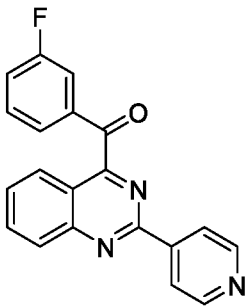
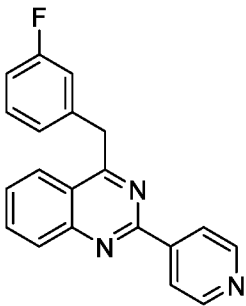
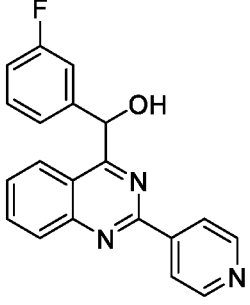
R^7 is H; and R^8 is selected from H and OH;

5 R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^B is C_{6-10} aryl, optionally substituted with halo; and

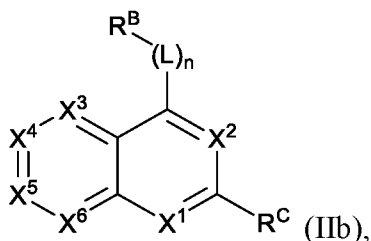
R^A is 5-10 membered heteroaryl, optionally substituted with halo, NO_2 , C_{1-6} alkyl, or C_{1-6} alkoxy.

10 In some embodiments, the compound of Formula (IIa) is selected from any one of the following compounds:

BC18615		BC18617	
BC18616			

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) has Formula (IIb):



15

or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from O, S, $\text{S}(=\text{O})_2$, C_{1-3} alkylene, $\text{C}(=\text{O})$, and $\text{N}(\text{R}^N)$, wherein said C_{1-3} alkylene is optionally substituted with 1, 2, or 3 substituents

independently selected from halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

each R^N is independently selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{dl};

n is an integer selected from 1, 2, and 3;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

X³ is selected from N, N⁺-O⁻, and CR³;

X⁴ is selected from N, N⁺-O⁻, and CR⁴;

X⁵ is selected from N, N⁺-O⁻, and CR⁵;

X⁶ is selected from N, N⁺-O⁻, and CR⁶;

provided that no more than four of X¹, X², X³, X⁴, X⁵, and X⁶ are N;

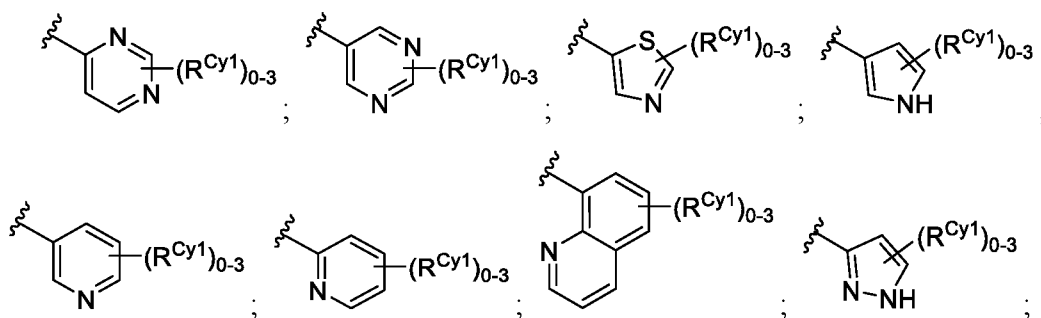
each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{dl}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{dl};

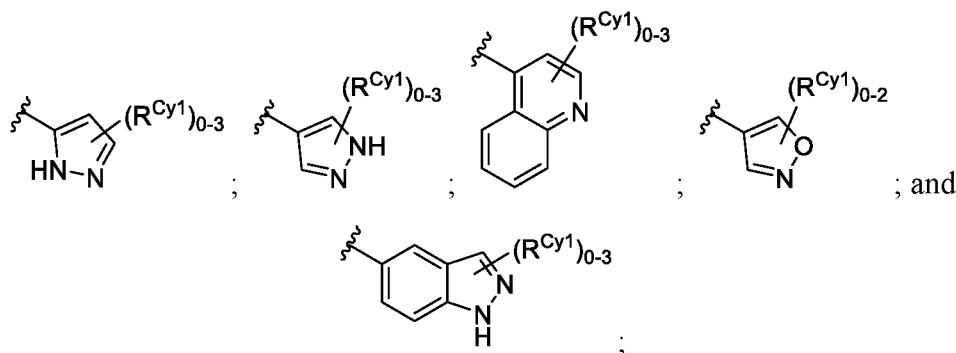
R^C is selected from:

(i) 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}; and

(ii) a group selected from O-Cy^{A1}, N(R^N)-Cy^{A1}, and Cy^{A1};

each Cy^{A1} is a 5-10 membered heteroaryl group of the formula selected from:





R^B is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} .

R^{Cy1} and R^{Cy2} are each independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

each Cy² is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

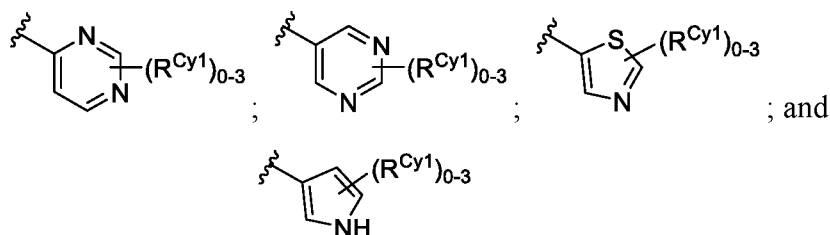
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

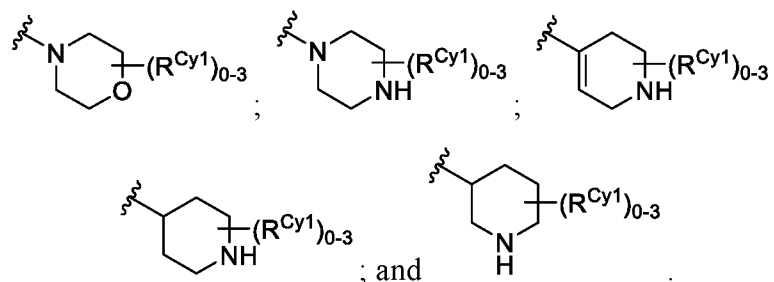
each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl,

di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

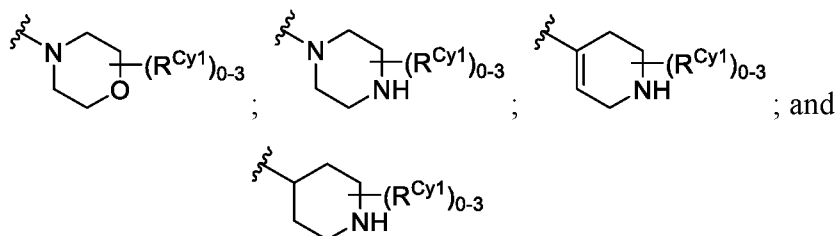
In some embodiments, R^C is selected from 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}; and a 5-10 membered heteroaryl group of the formula selected from:



In some embodiments of the compound of Formula (IIb), the 4-10 membered heterocycloalkyl of R^C has the formula selected from:



In some embodiments of the compound of Formula (IIb), the 4-10 membered heterocycloalkyl of R^C has the formula selected from:



In some embodiments of the compound of Formula (IIb):

n is 1;

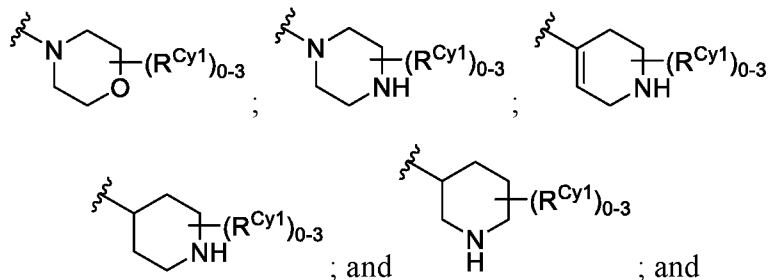
L is selected from C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with OH;

R^N is selected from H and C₁₋₆ alkyl;

R¹, R², R³, R⁴, R⁵, and R⁶ are each independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{al}, NR^{c1}R^{d1}, and S(O)₂R^{b1};

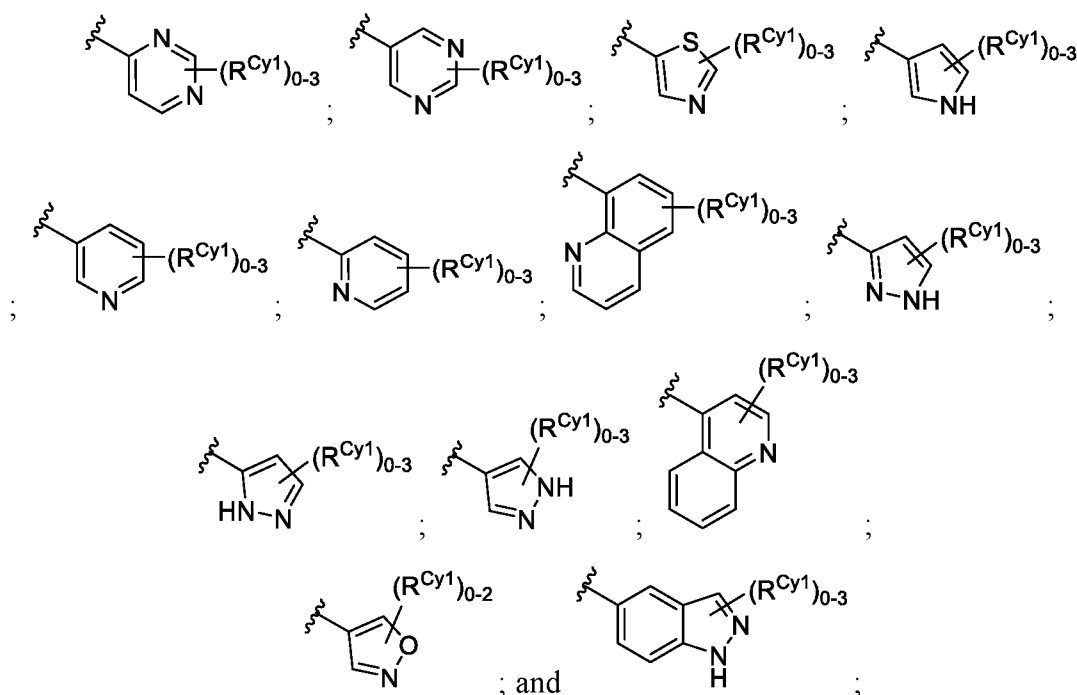
R^C is selected from:

(i) 4-10 membered heterocycloalkyl selected from:



5

(ii) a group selected from $O-Cy^{A1}$, $N(R^N)-Cy^{A1}$, and Cy^{A1} , wherein each Cy^{A1} is a 5-10 membered heteroaryl group of the formula selected from:



10

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} ;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

In some embodiments of the compound of Formula (IIb):

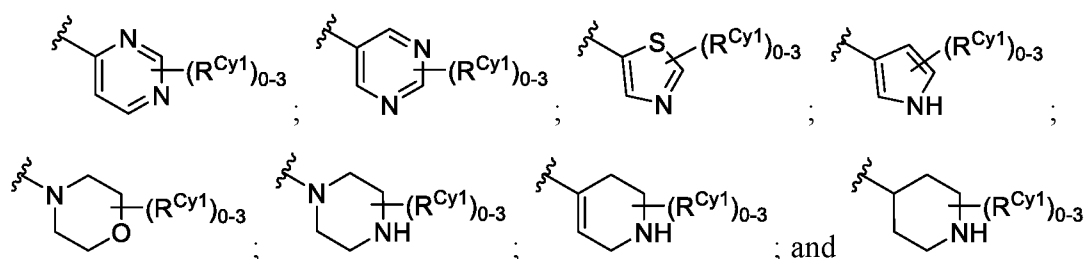
n is 1;

5 L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^N is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and OR^{a1} ;

10 R^C is selected from:



15 R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to L which is $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

20 each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

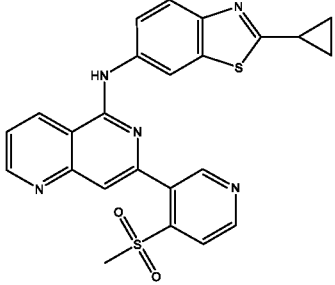
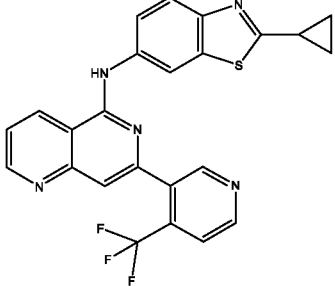
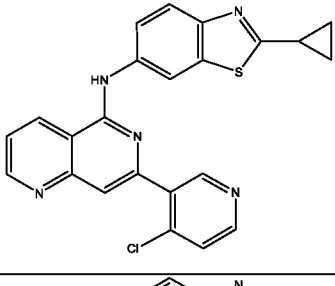
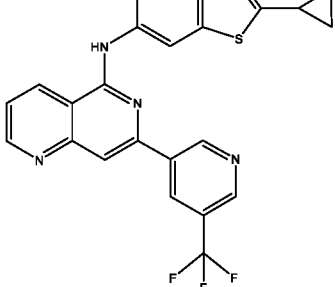
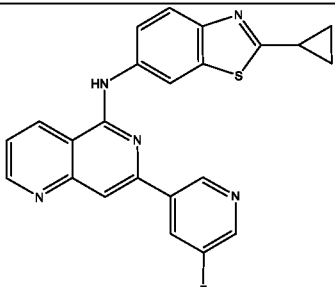
25 In some embodiments, the compound of Formula (IIb) is selected from any one of the following compounds:

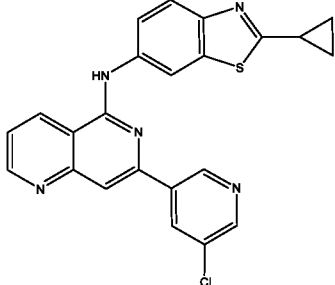
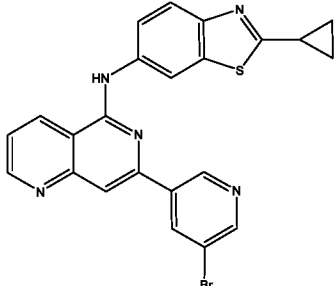
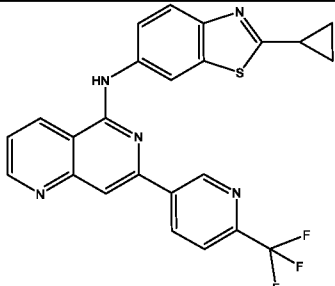
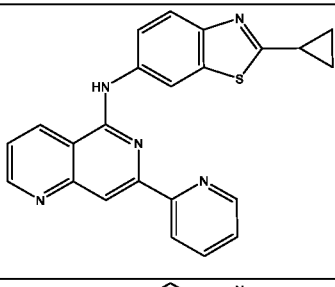
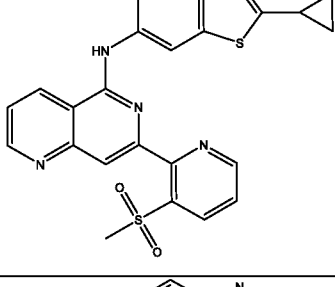
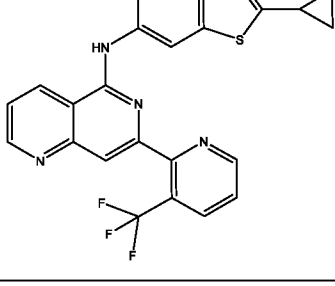
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BC18670	
BC18702	
BC18703	

BC18704	
BC18705	
BC18706	
BC18720	
BC18722	

BC18738	
BC18740	
BC18742	
BC18853	
BC18854	
BC191107	

BC191108	
BC191109	
BC191110	
BC191111	
BC191112	
BC191113	

BC191114	
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BC191116	
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BC191119	
BC191120	
BC191121	
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BC191123	
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BC191125	
BC191126	
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BC191128	
BC191129	

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BC18831	

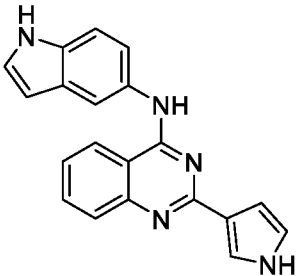
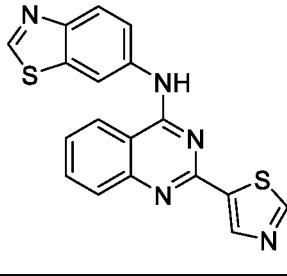
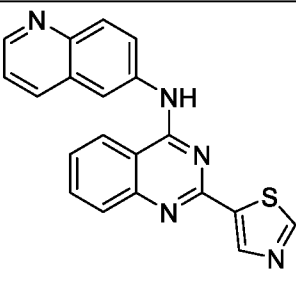
BC18832	
BC18833	
BC18834	
BC18835	
BC18836	

BC18838	
BC18839	
BC18840	
BC18841	
BC18845	

or a pharmaceutically acceptable salt thereof.

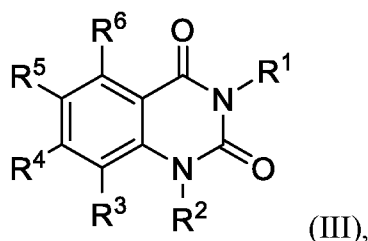
In some embodiments, the compound of Formula (IIb) is selected from any one of the following compounds:

BC18618	
BC18664	
BC18666	
BC18670	
BC18702	
BC18703	
BC18704	
BC18705	
BC18706	
BC18720	
BC18722	

BC18738		BC18742	
BC18740			

or a pharmaceutically acceptable salt thereof.

In some embodiments, the document provides a compound of Formula (III):



5 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$,

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$,

R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN,

NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},
NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10
membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is
optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from
R^{Cy2};

each R^{Cy2} is independently selected from halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆
haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2},
NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};
wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted
with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a2}, and
C(O)R^{b2}, C(O)NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H,
C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10
membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀
cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10
membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered
heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10
membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄
alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently
selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a
4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3
substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a
4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3
substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆
alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene,
HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered
heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-
C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered
heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆

alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments, R¹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹.

In some embodiments, R¹ is C₁₋₆ alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹.

In some embodiments, R¹ is Cy¹.

In some embodiments, R¹ is C₂₋₆ alkenyl.

In some embodiments, R² is selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, C(O)NR^{c1}R^{d1}, and NR^{c1}R^{d1}.

In some embodiments, R² is H.

In some embodiments, R² is C₁₋₆ alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, C(O)NR^{c1}R^{d1}, and NR^{c1}R^{d1}.

In some embodiments, R² is C₁₋₆ alkyl, optionally substituted with Cy¹.

In some embodiments, R² is C₁₋₆ alkyl, optionally substituted with C(O)NR^{c1}R^{d1} or NR^{c1}R^{d1}.

In some embodiments, R² is C₁₋₆ alkyl, optionally substituted with C(O)NR^{c1}R^{d1}.

In some embodiments, R² is C₁₋₆ alkyl, optionally substituted with NR^{c1}R^{d1}. In some embodiments, R^{c1} and R^{d1} are each H. In some embodiments, R^{c1} and R^{d1} are each C₁₋₆ alkyl. In some embodiments, R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, R³, R⁴, R⁵, and R⁶ are each independently selected from H and C(O)NR^{c1}R^{d1}.

In some embodiments, R³ and R⁶ are each H.

In some embodiments, R⁴ is C(O)NR^{c1}R^{d1}. In some embodiments, R³, R⁵, and R⁶ are each H. In some embodiments, R⁵ is C(O)NR^{c1}R^{d1}. In some embodiments, R³,

R^4 , and R^6 are each H. In some embodiments, R^{c1} is H and R^{d1} is selected from C_{6-10} aryl- C_{1-4} alkylene and (5-10 membered heteroaryl)- C_{1-4} alkylene.

In some embodiments, each Cy^1 is independently selected from C_{6-10} aryl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, Cy^1 is C_{6-10} aryl (e.g., phenyl), optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, Cy^1 is 4-10 membered heterocycloalkyl (e.g., pyrrolidinyl, morpholinyl), optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

In some embodiments, each R^{Cy2} is independently selected from halo, CN, C_{1-6} alkyl, OR^{a2} ; wherein said C_{1-6} alkyl is optionally substituted with $C(O)NR^{c2}R^{d2}$.

In some embodiments, R^{Cy2} is halo.

In some embodiments, R^{Cy2} is CN, C_{1-6} alkyl, or C_{1-6} alkoxy.

In some embodiments, R^{Cy2} is C_{1-6} alkyl, optionally substituted $C(O)NR^{c2}R^{d2}$. In some embodiments, R^{c2} is H, and R^{d2} is selected from C_{6-10} aryl, 5-10 membered heteroaryl, C_{6-10} aryl- C_{1-4} alkylene, and (5-10 membered heteroaryl)- C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g .

In some embodiments, each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{6-10} aryl- C_{1-4} alkylene, and (5-10 membered heteroaryl)- C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{6-10} aryl- C_{1-4} alkylene, and (5-10 membered heteroaryl)- C_{1-4} alkylene, are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g .

In some embodiments, each R^g is independently selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments:

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 ;

R^2 is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$;

R^3 , R^4 , R^5 , and R^6 are each independently selected from H and $C(O)NR^{c1}R^{d1}$;

Cy¹ is independently selected from C₆₋₁₀ aryl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2};

R^{Cy2} is independently selected from halo, CN, C₁₋₆ alkyl, and OR^{a2}; wherein
 5 said C₁₋₆ alkyl is optionally substituted with C(O)NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl-C₁₋₄ alkylene, and (5-10 membered heteroaryl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl-C₁₋₄ alkylene, and (5-10 membered heteroaryl)-C₁₋₄
 10 alkylene are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy.

In some embodiments, the compound of Formula (III) is any one of the compounds provided in Table 4, or a pharmaceutically acceptable salt thereof.

15 In some embodiments, a salt of a compound of any Formulae disclosed herein is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

20 In some embodiments, acids commonly employed to form pharmaceutically acceptable salts of the compounds of any Formulae disclosed herein include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic
 25 acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate,
 30

methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment,
5 pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid.

In some embodiments, bases commonly employed to form pharmaceutically acceptable salts of the compounds of any Formulae include hydroxides of alkali
10 metals, including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C1-C6)-
15 alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like.

In some embodiments, the compounds of any Formulae disclosed herein, or pharmaceutically acceptable salts thereof, are substantially isolated.

20 In some embodiments, a compound of any Formulae disclosed herein, or a pharmaceutically acceptable salt thereof, can have the ability to increase TFEB polypeptide levels within a cell and/or within a nucleus of a cell. Such cells can be *in vitro* or *in vivo*. For example, a compound of any Formulae disclosed herein, or a pharmaceutically acceptable salt thereof, can have the ability to increase TFEB
25 polypeptide levels within the nucleus of cells present within a mammal (e.g., a human) following administration to that mammal.

Methods of making therapeutic compounds

Compounds of any one of the Formulae disclosed herein, including salts
30 thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes. For example, the compounds described herein can be prepared using methods and procedures similar to those described in the Examples 1a-1p herein. A person skilled in the art knows how to select and implement appropriate synthetic protocols, and appreciates that the

processes described are not the exclusive means by which compounds provided herein may be synthesized, and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds provided herein.

Suitable synthetic methods of starting materials, intermediates, and products can be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic Chemistry*, Vols. 1-107 (Elsevier, 1963-2012); *Journal of Heterocyclic Chemistry* Vols. 1-49 (*J. Heterocyclic Chemistry*, 1964-2012); Carreira *et al.*, (Ed.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky *et al.*, (Ed.) *Comprehensive Organic Functional Group Transformations*, (Pergamon Press, 1996); Katritzky *et al.*, (Ed.) *Comprehensive Organic Functional Group Transformations II* (Elsevier, 2nd Edition, 2004); Katritzky *et al.*, (Ed.) *Comprehensive Heterocyclic Chemistry* (Pergamon Press, 1984); Katritzky *et al.*, *Comprehensive Heterocyclic Chemistry II*, (Pergamon Press, 1996); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Trost *et al.* (Ed.) *Comprehensive Organic Synthesis* (Pergamon Press, 1991).

The reactions for preparing the compounds provided herein can be carried out in suitable solvents that can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of the compounds provided herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, 4th Ed., Wiley & Sons, Inc., New York (2006).

Pharmaceutical compositions and formulations

This document also provides pharmaceutical compositions comprising an effective amount of a compound of any one of Formulae (I)-(III) disclosed herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

5 The pharmaceutical composition also can comprise any one of the additional therapeutic agents and/or therapeutic molecules described herein. The carrier(s) are “acceptable” in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

10 Pharmaceutically acceptable carriers, adjuvants, and vehicles that can be used in the pharmaceutical compositions provided herein include, without limitation, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (e.g., human serum albumin), buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or
15 electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wool fat.

20 The compositions or dosage forms can contain any one or more of the compounds or therapeutic agents described herein in the range of 0.005 percent to 100 percent with the balance made up from the suitable pharmaceutically acceptable carriers or excipients. The contemplated compositions can contain from about 0.001 percent to about 100 percent (e.g., from about 0.1 percent to about 95 percent, from
25 about 75 percent to about 85 percent, or from about 20 percent to about 80 percent) of any one or more of the compounds or therapeutic agents provided herein, wherein the balance can be made up of any pharmaceutically acceptable carrier or excipient described herein, or any combination of these carriers or excipients.

Routes of administration and dosage forms

30 The therapeutic compounds and/or pharmaceutical compositions provided herein (e.g., a composition containing one or more compounds set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) can include those suitable for any acceptable route of administration. Acceptable routes of

administration include, without limitation, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intranasal, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral, vaginal, intravitreal, subretinal or other intraocular routes of administrations.

Compositions and formulations described herein can conveniently be presented in a unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and can be prepared by any methods well known in the art of pharmacy.

See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000). Such preparative methods include, without limitation, the step of bringing into association with the molecule to be administered ingredients such as a carrier that constitutes one or more accessory ingredients. In general, the compositions can be prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In some embodiments, any one or more of the compounds or therapeutic agents described herein can be administered orally. Compositions described herein that are suitable for oral administration can be presented as discrete units such as capsules, sachets, granules, or tablets each containing a predetermined amount (e.g., effective amount) of the active ingredient(s); a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus. Soft gelatin capsules can be useful for containing such suspensions, which can beneficially increase the rate of compound absorption. In the case of tablets for oral use, carriers that are commonly used include, without limitation, lactose, sucrose, glucose, mannitol, silicic acid, and starches. Other acceptable excipients can include, without limitation, (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as carboxymethylcellulose, alginates, gelatin,

polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. For oral administration in a capsule form, useful diluents include, without limitation, lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient(s) can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents can be added. Compositions suitable for oral administration include, without limitation, lozenges comprising ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient(s) in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include, without limitation, aqueous and non-aqueous sterile injection solutions or infusion solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The formulations can be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injections, saline (e.g., 0.9% saline solution), or 5% dextrose solution, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets. The injection solutions can be in the form of, for example, a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. A sterile injectable preparation also can be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils can be used as a solvent or suspending medium. For this purpose, any bland fixed oil can be

used including, without limitation, synthetic mono- or diglycerides. Fatty acids such as oleic acid and its glyceride derivatives can be used to prepare injectables. In some cases, natural pharmaceutically acceptable oils such as olive oil or castor oil, especially in their polyoxyethylated versions, can be used to prepare injectables.

5 These oil solutions or suspensions also can contain a long-chain alcohol diluent or dispersant.

In some cases, a therapeutic compound and/or pharmaceutical composition provided herein can be administered in the form of suppository for rectal administration. These compositions can be prepared by mixing a compound
10 described herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) with a suitable non-irritating excipient that is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active component(s). Such materials include, without limitation, cocoa butter, beeswax, and polyethylene glycols.

15 In some cases, a therapeutic compounds and/or pharmaceutical composition provided herein can be administered by nasal aerosol or inhalation. Such compositions can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance
20 bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, U.S. Patent No. 6,803,031. Additional formulations and methods for intranasal administration are found in Ilium, L., *J. Pharm. Pharmacol.*, 56:3-17 (2004); and Ilium, L., *Eur. J. Pharm. Sci.*, 11:1-18 (2000).

In some cases, a therapeutic compounds and/or pharmaceutical composition
25 provided herein can be prepared as a topical composition and used in the form of an aerosol spray, cream, emulsion, solid, liquid, dispersion, foam, oil, gel, hydrogel, lotion, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, towelette, soap, or other forms commonly employed in the art of topical administration and/or cosmetic and skin care formulation. The topical compositions
30 can be in an emulsion form. Topical administration of a therapeutic compounds and/or pharmaceutical composition provided herein can be useful when the desired treatment involves areas or organs readily accessible by topical application. In some cases, a topical composition can include a combination of any one or more of the compounds or therapeutic agents described herein (e.g., a compound set forth in

Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof), and one or more additional ingredients, carriers, excipients, or diluents including, without limitation, absorbents, anti-irritants, anti-acne agents, preservatives, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents, silicones, skin-identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

In some cases, one or more compounds or therapeutic agent described herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can be incorporated into a composition for coating an implantable medical device such as a prosthesis, artificial valve, vascular graft, stent, or catheter. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Patent Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings can be biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, or mixture thereof. In some cases, the coating can optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

In some cases, this document provides an implantable drug release device impregnated with or containing one or more compounds or therapeutic agents described herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) such that the compound(s) or therapeutic agent(s) are released from the device and are therapeutically active.

Dosages and regimens

A composition (e.g., pharmaceutical compositions provided herein) containing a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) can include that compound in an effective amount (e.g., a therapeutically effective amount).

Effective doses can vary, depending on the diseases being treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents, and the judgment of the treating physician.

In some embodiments, an effective amount of a compound of any one of Formulae (I)-(III), or a pharmaceutically acceptable salt thereof, can range, for example, from about 0.1 mg to about 1000 mg. In some cases, the effective amount can be from about 0.5 mg to about 500 mg of a compound disclosed herein, or any amount in between these two values, for example, one of about 0.5 mg, about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. The effective amount can be an amount sufficient to alleviate or reduce one or more of the symptoms associated with a disease, disorder, or condition being treated as described herein.

In some cases, an effective amount of a compound of any one of Formulae (I)-(III), or a pharmaceutically acceptable salt thereof, can range, for example, from about 0.001 mg/kg to about 500 mg/kg (e.g., from about 0.001 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 150 mg/kg; from about 0.01 mg/kg to about 100 mg/kg; from about 0.01 mg/kg to about 50 mg/kg; from about 0.01 mg/kg to about 10 mg/kg; from about 0.01 mg/kg to about 5 mg/kg; from about 0.01 mg/kg to about 1 mg/kg; from about 0.01 mg/kg to about 0.5 mg/kg; from about 0.01 mg/kg to about 0.1 mg/kg; from about 0.1 mg/kg to about 200 mg/kg; from about 0.1 mg/kg to about 150 mg/kg; from about 0.1 mg/kg to about 100 mg/kg; from about 0.1 mg/kg to about 50 mg/kg; from about 0.1 mg/kg to about 10 mg/kg; from about 0.1 mg/kg to about 5 mg/kg; from about 0.1 mg/kg to about 2 mg/kg; from about 0.1 mg/kg to about 1 mg/kg; from about 0.1 mg/kg to about 0.5 mg/kg, or from about 0.5 mg/kg to about 500 mg/kg).

In some cases, an effective amount of a compound of any one of Formulae (I)-(III), or a pharmaceutically acceptable salt thereof, can be about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, or about 5 mg/kg.

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses, e.g., once daily, twice daily, thrice daily) or on a non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weekly, once every two weeks, or once a month). In some cases, the dosages can be administered every 4 hours, 6 hours, 8 hours, 12 hours, or 24 hours.

Kits

This document also provides pharmaceutical kits useful, for example, to increase TFEB polypeptide levels within cells and/or within the nucleus of cells within a mammal (e.g., a human). In some cases, this document provides pharmaceutical kits useful, for example, to treat diseases, disorders, and conditions referred to herein. Such pharmaceutical kits can include one or more containers containing a pharmaceutical composition that includes a therapeutically effective amount of a compound provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof). In some cases, such kits can further include, if desired, one or more of various conventional pharmaceutical kit components such as containers with one or more pharmaceutically acceptable carriers. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components also can be included in a kit provided herein.

Combination therapy

In some cases, one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) can be combined with one or more therapeutic molecules. Examples of therapeutic molecules that can be used in combination with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) include, without limitation, enzyme replacement therapy (e.g., approved enzyme therapy) for LSDs (e.g., fabrazyme or cerezyme). In such cases, the addition of one or more such compounds can aid in the treatment of central nervous system disease not approachable by enzyme replacement therapy due to the restriction imposed by the blood-brain barrier to serum proteins. In some cases, the addition of one or more such compounds can increase the cellular uptake of a given lysosomal enzyme replacement therapeutic protein in the periphery by augmenting expression of the mannose-6-phosphate receptor, a TFEB transcriptional target, and the receptor-mediated mechanism through which enzyme replacement therapies gain entry into a disease cell or tissue. Additional examples of therapeutic molecules that can be used in combination with one or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-III), or (III), or a pharmaceutically acceptable salt thereof) include, without limitation, anti-

inflammatory agents (e.g., steroids and antibodies against IL-6 or TNF-alpha), antimicrobial agents (e.g., antibiotics, anti-mycobacterial drugs, and anti-viral agents), anti-cancer agents (e.g., chemotherapeutic agents and cellular products such as engineered T cells), anti-aging agents (e.g., nicotinamide riboside, or rapamycin), neurological agents (e.g., L-DOPA, memantine, and riluzole), therapies for a neurodegenerative disease (e.g., edaravone or tetrabenazine), and agents used to treat chronic organ dysfunction (e.g., ACE inhibitor and lactulose).

One or more compounds provided herein (e.g., a compound set forth in Formula (I), (IIa-IIi), or (III), or a pharmaceutically acceptable salt thereof) and the one or more therapeutic molecules can be administered in any order or simultaneously. If simultaneously administered, they can be provided in a single, unified, form or in multiple forms (e.g., either as a single pill or as two separate pills). One of the items can be given in multiple doses, or both can be given as multiple doses. If not simultaneous, the timing between the multiple doses can vary from more than zero weeks to less than four weeks.

Definitions

As used herein, the term “about” means “approximately” (e.g., plus or minus approximately 10% of the indicated value).

At various places in this document, substituents of compounds provided herein are disclosed in groups or in ranges. It is specifically intended that these groups and ranges include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

At various places in this document various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term “a pyridine ring” or “pyridinyl” may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

It is further appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features described herein which are, for brevity, described in the context of a single embodiment, also can be provided separately or in any suitable subcombination.

The term “aromatic” refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (i.e., having $(4n + 2)$ delocalized π (pi) electrons where n is an integer).

The term “ n -membered” where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n . For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the phrase “optionally substituted” means unsubstituted or substituted. The substituents are independently selected, and substitution can be at any chemically accessible position. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms. It is to be understood that substitution at a given atom is limited by valency.

Throughout the definitions, the term “ C_{n-m} ” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4} , C_{1-6} , and the like.

As used herein, the term “ C_{n-m} alkyl”, employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, without limitation, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

As used herein, the term “ C_{n-m} haloalkyl”, employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to $2s+1$ halogen atoms that may be the same or different, where “ s ” is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, “ C_{n-m} alkenyl” refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. Example alkenyl groups

include, without limitation, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, “C_{n-m} alkynyl” refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, without limitation, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylene”, employed alone or in combination with other terms, refers to a divalent alkyl-linking group having n to m carbons. Examples of alkylene groups include, without limitation, ethan-1,1-diyl, ethan-1,2-diyl, propan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl, and the like. In some embodiments, the alkylene moiety contains 2 to 6, 2 to 4, 2 to 3, 1 to 6, 1 to 4, or 1 to 2 carbon atoms.

As used herein, the term “C_{n-m} alkoxy”, employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include, without limitation, methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), butoxy (e.g., *n*-butoxy and *tert*-butoxy), and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, “C_{n-m} haloalkoxy” refers to a group of formula -O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF₃. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “amino” refers to a group of formula -NH₂.

As used herein, the term “C_{n-m} alkylamino” refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkylamino groups include, without limitation, N-methylamino, N-ethylamino, N-propylamino (e.g., N-(*n*-propyl)amino and N-isopropylamino), N-butylamino (e.g., N-(*n*-butyl)amino and N-(*tert*-butyl)amino), and the like.

As used herein, the term “di(C_{n-m}-alkyl)amino” refers to a group of formula -N(alkyl)₂, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkoxy carbonyl” refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkoxy carbonyl groups include, without limitation, methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl (e.g., *n*-propoxy carbonyl and isopropoxy carbonyl), butoxy carbonyl (e.g., *n*-butoxy carbonyl and *tert*-butoxy carbonyl), and the like.

As used herein, the term “C_{n-m} alkyl carbonyl” refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkyl carbonyl groups include, without limitation, methyl carbonyl, ethyl carbonyl, propyl carbonyl (e.g., *n*-propyl carbonyl and isopropyl carbonyl), butyl carbonyl (e.g., *n*-butyl carbonyl and *tert*-butyl carbonyl), and the like.

As used herein, the term “C_{n-m} alkyl carbonylamino” refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkyl sulfonylamino” refers to a group of formula -NHS(O)₂-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminosulfonyl” refers to a group of formula -S(O)₂NH₂.

As used herein, the term “C_{n-m} alkyl aminosulfonyl” refers to a group of formula -S(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl) aminosulfonyl” refers to a group of formula -S(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminosulfonylamino” refers to a group of formula -NHS(O)₂NH₂.

As used herein, the term “C_{n-m} alkyl aminosulfonylamino” refers to a group of formula -NHS(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl) aminosulfonylamino” refers to a group of formula -NHS(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m

carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminocarbonylamino”, employed alone or in combination with other terms, refers to a group of formula -NHC(O)NH_2 .

5 As used herein, the term “ C_{n-m} alkylaminocarbonylamino” refers to a group of formula -NHC(O)NH(alkyl) , wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “ $\text{di(C}_{n-m}\text{ alkyl)aminocarbonylamino}$ ” refers to a group of formula -NHC(O)N(alkyl)_2 , wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6,
10 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “carbamyl” to a group of formula -C(O)NH_2 .

As used herein, the term “ C_{n-m} alkylcarbamyl” refers to a group of formula -C(O)-NH(alkyl) , wherein the alkyl group has n to m carbon atoms. In some
15 embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “ $\text{di(C}_{n-m}\text{-alkyl)carbamyl}$ ” refers to a group of formula -C(O)N(alkyl)_2 , wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

20 As used herein, the term “thio” refers to a group of formula -SH .

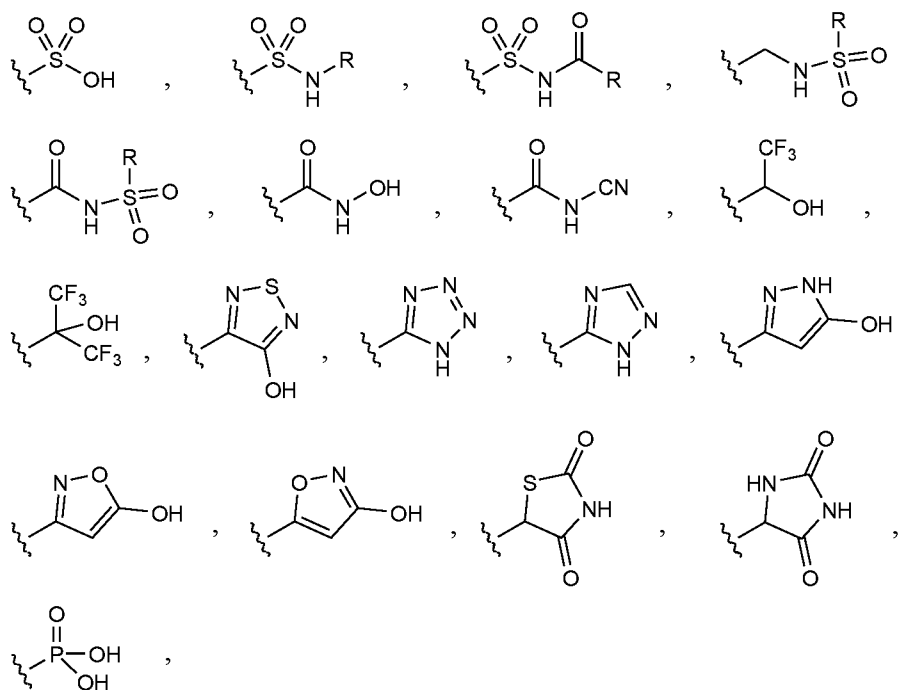
As used herein, the term “ C_{n-m} alkylthio” refers to a group of formula -S-alkyl , wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “ C_{n-m} alkylsulfinyl” refers to a group of formula -S(O)-alkyl , wherein the alkyl group has n to m carbon atoms. In some
25 embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “ C_{n-m} alkylsulfonyl” refers to a group of formula $\text{-S(O)}_2\text{-alkyl}$, wherein the alkyl group has n to m carbon atoms. In some
embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

30 As used herein, the term “carbonyl”, employed alone or in combination with other terms, refers to a -C(=O)- group, which may also be written as C(O) .

As used herein, the term “carboxy” refers to a -C(O)OH group. In some embodiments, the “carboxy” group also refers to a bioisostere replacement group selected from the group consisting of:



and the like, where R refers to a hydrogen, (C₁-C₈) alkyl, or C₆ aryl.

As used herein, the term “cyano-C₁₋₃ alkyl” refers to a group of formula -(C₁₋₃ alkylene)-CN.

5 As used herein, the term “HO-C₁₋₃ alkyl” refers to a group of formula -(C₁₋₃ alkylene)-OH.

As used herein, “halo” refers to F, Cl, Br, or I. In some embodiments, a halo is F, Cl, or Br.

As used herein, the term “aryl,” employed alone or in combination with other
 10 terms, refers to an aromatic hydrocarbon group, which can be monocyclic or polycyclic (e.g., having 2, 3, or 4 fused rings). The term “C_{n-m} aryl” refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some
 15 embodiments, aryl groups can have from 6 to 10 carbon atoms. In some embodiments, the aryl group is phenyl or naphthyl.

As used herein, “cycloalkyl” refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3, or 4 fused rings) groups and spirocycles. Ring-
 20 forming carbon atoms of a cycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfide groups (e.g., C(O) or C(S)). Also included in the definition of cycloalkyl are moieties that have one or more aromatic or non-aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for

example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. A cycloalkyl group may contain a fused heterocycloalkyl ring which itself may be fused with another ring such as an aromatic ring. In this situation, the cycloalkyl group can be attached through any ring forming atom, including ring forming atoms of the heterocycloalkyl ring or the aromatic ring. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (C₃₋₁₀). Cycloalkyl groups can also have 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 ring-forming atoms (carbon atoms or heteroatoms if the cycloalkyl group is fused with a heterocycloalkyl ring) (C₃₋₁₄ cycloalkyl). In some embodiments, the cycloalkyl is a C₃₋₁₀ monocyclic or bicyclic cycloalkyl. In some embodiments, the cycloalkyl is a C₃₋₇ monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C₃₋₁₄ bicyclic or tricyclic cycloalkyl. Example cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, “heteroaryl” refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl is a 5-10 membered monocyclic or bicyclic heteroaryl having 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, the heteroaryl is a 5-14 membered monocyclic, bicyclic, or tricyclic heteroaryl having 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, the heteroaryl is a 5-6 monocyclic heteroaryl having 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls include, without limitation, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl,

isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl. A six-membered heteroaryl ring is a heteroaryl with a ring having six ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls include, without limitation, pyridyl, pyrazinyl, pyrimidinyl, triazinyl, and pyridazinyl.

As used herein, “heterocycloalkyl” refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl groups. Included in heterocycloalkyl are mono-, bi-, tri-, and tetracyclic 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles. Example heterocycloalkyl groups include, without limitation, pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropyran, oxetanyl, azetidiny, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfido groups (e.g., C(O), S(O), C(S), or S(O)₂, etc.). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic or non-aromatic rings fused (i.e., having a bond in common with) to the heterocycloalkyl ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 4-10 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring can be attached at any position of the ring, whereas a
5 pyridin-3-yl ring is attached at the 3-position.

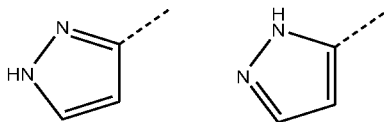
As used herein, the term “oxo” refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to a carbon (e.g., C=O), or attached to a heteroatom forming a sulfoxide or sulfone group.

The term “compound” as used herein is meant to include all stereoisomers,
10 geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are
15 intended unless otherwise indicated. Compounds provided herein that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Any appropriate method can be used to prepare optically active forms from, for example, optically inactive starting materials. For example, techniques such as resolution of racemic mixtures or stereoselective synthesis can be used to prepare
20 optically active forms of a compound provided herein. Many geometric isomers of olefins, C=N double bonds, N=N double bonds, and the like also can be present in a compound described herein, and all such stable isomers are contemplated herein. *Cis* and *trans* geometric isomers of the compounds provided herein are described and can be isolated as a mixture of isomers or as separated isomeric forms. In some
25 embodiments, a compound provided herein has the (*R*)-configuration. In some embodiments, a compound provided herein has the (*S*)-configuration.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic
30 tautomers that are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include, without limitation, ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H-, and 4H-1,2,4-triazole, 1H- and

2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. For example, in aqueous solution, pyrazoles can exhibit the following isomeric forms, which are referred to as tautomers of each other:



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As readily understood by one skilled in the art, a wide variety of functional groups and other structures can exhibit tautomerism, and all tautomers of compounds as described herein are within the scope provided herein.

As used herein, the term “cell” is meant to refer to a cell that is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal (e.g., a human). In some embodiments, an *in vitro* cell can be a cell in cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal (e.g., a human).

As used herein, the term “contacting” refers to the bringing together of indicated moieties or items in an *in vitro* system, an *ex vivo* system, or an *in vivo* system. For example, “contacting” a cell with a compound provided herein includes the act of administering that compound to a mammal (e.g., a human) containing that cell as well as, for example, introducing that compound into a cell culture containing that cell.

As used herein, the term “mammal” includes, without limitation, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, elephants, deer, non-human primates (e.g., monkeys and apes), house pets, and humans.

As used herein, the phrase “effective amount” or “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, mammal, or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician.

As used herein, the term “treating” or “treatment” refers to (a) inhibiting a disease, disorder, or condition, for example, inhibiting a disease, disorder, or condition in a mammal (e.g., human) that is experiencing or displaying the pathology or symptomatology of the disease, disorder, or condition (e.g., arresting further development of the pathology and/or symptomatology), or (b) ameliorating the disease, disorder, or condition, for example, ameliorating a disease, disorder, or

condition in a mammal (e.g., a human) that is experiencing or displaying the pathology or symptomatology of the disease, disorder, or condition (e.g., reversing the pathology and/or symptomatology).

As used herein, the term “preventing” or “prevention” of a disease, disorder, or condition refers to decreasing the risk of occurrence of the disease, disorder, or condition in a mammal or group of mammals (e.g., a mammal or group of mammals predisposed to or susceptible to the disease, disorder, or condition). In some embodiments, preventing a disease, disorder, or condition refers to decreasing the possibility of acquiring the disease, disorder, or condition and/or its associated symptoms. In some embodiments, preventing a disease, disorder, or condition refers to completely or almost completely stopping the disease, disorder, or condition from occurring.

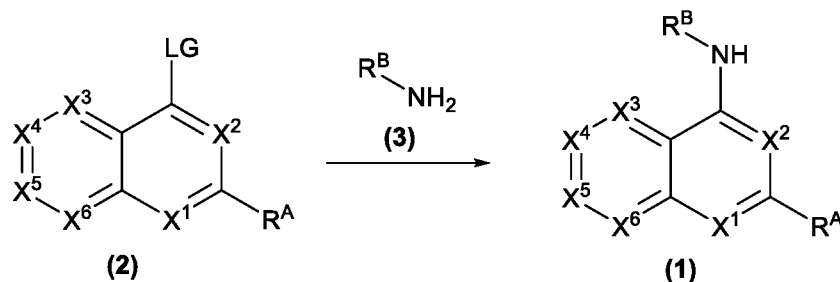
EXAMPLES

Material and methods

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl solutions; anhydrous dichloromethane and toluene were distilled from CaH_2 ; alternatively, the same solvents were obtained from a solvent purification system using alumina columns. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Reactions were monitored via TLC using 250 μm pre-coated silica gel 60 F254 plates, which were visualized with 254 nm and/or 365 nm UV light and by staining with KMnO_4 (1.5 g KMnO_4 , 10 g K_2CO_3 , and 1.25 mL 10% NaOH in 200 mL water), cerium molybdate (0.5 g $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$, 12 g $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$, and 28 mL conc. H_2SO_4 in 235 mL water), or vanillin (6 g vanillin and 1.5 mL conc. H_2SO_4 in 100 mL EtOH). Flash chromatography was performed with SiliCycle silica gel 60 (230-400 mesh) or with ISCO MPLC. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400, or 500 MHz spectrometers, using the residual solvent as an internal standard. IR spectra were obtained on a Smiths IdentifyIR or PerkinElmer Spectrum 100. HRMS data were obtained on a Thermo Scientific Exactive HRMS coupled to a Thermo Scientific Accela HPLC system using a 2.1 x 50 mm 3.5 μm Waters XTerra C18 column eluting with $\text{MeCN}/\text{H}_2\text{O}$ containing 0.1% formic acid. Purity of compounds was assessed

using the same HPLC system with either the PDA or an Agilent 385 ELSD. All final screening samples passed QC based on >95% purity by LC/MS/ELSD analysis.

General synthetic scheme



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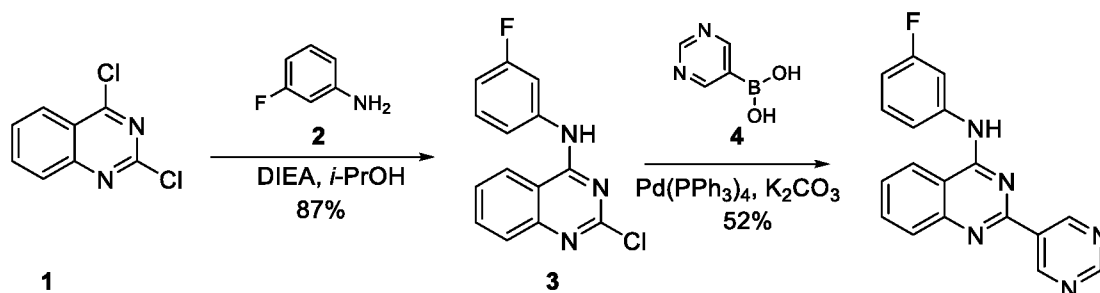
By way of example, to prepare the compounds of Formula (I) where n is 1 and L is NH (1), equimolar amounts of 4-chloroquinazoline analog (2) and an amine (3) are mixed in a suitable solvent (e.g., isopropanol). The resultant reaction mixture is stirred and refluxed for, e.g., 4 hours. Progression of the reaction is monitored by techniques known in the art. Upon consumption of the starting material, the reaction mixture is concentrated, and the target compound is purified through prep-TLC or flash chromatography. Products can be further purified by crystallization as is customary in the art. Referring to the general scheme, X¹, X², X³, X⁴, X⁵, X⁶, R^A, and R^B are as described herein, and LG is a leaving group (e.g., Cl, Br, I, or OTf). The compounds of Formula (I) where L is other than NH can be prepared from similar starting materials using reactions and synthetic routes well known in the art. A skill chemist would be able to select and implement appropriate reaction protocols and conditions.

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Example 1a – synthesis of compound 8 (BC18618)



Preparation of compound 3:

To a solution of **1** (1 g, 5.0 mmol, 1 eq) in *i*-PrOH (20 mL) was added **2** (615 mg, 5.5 mmol, 1.1 eq) and DIEA (1.29 g, 10 mmol, 2 eq). The reaction was stirred at

85 °C overnight. The mixture was concentrated and the residue was purified by silica column chromatography (PE/EA, 2:1) to give 1.2 g **3** (yellow oil, 87%). MS (ESI) m/z : 274 $[M+H]^+$

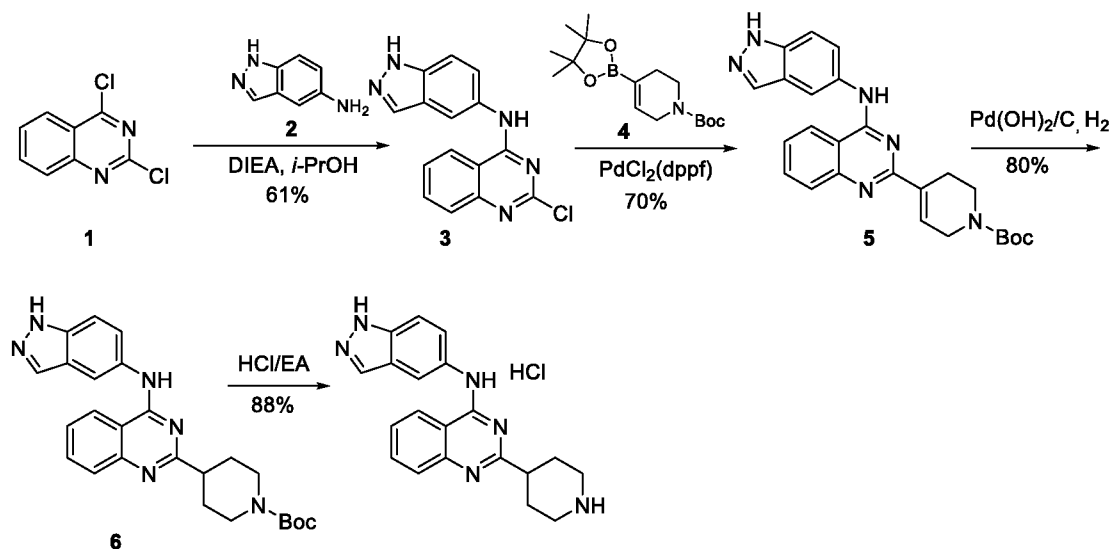
Preparation of compound 8 (BC18618)

To a solution of **3** (273 mg, 1 mmol, 1 eq) in dioxane/H₂O (1:1, 15 mL) was added **4** (248 mg, 2 mmol, 2 eq), K₂CO₃ (276 mg, 2 mmol, 2 eq) and Pd(PPh₃)₄ (124 mg, 0.1 mmol, 0.1 eq) under N₂. The mixture was stirred at 115 °C overnight. Then the mixture was filtered and the filter cake was washed by MeOH to give 205 mg **BC18618 (compound 8)** (off-white solid, 52%).

MS (ESI) m/z : 318 $[M+H]^+$, 316 $[M-H]^-$

¹H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 9.57 (s, 2H), 9.28 (s, 1H), 8.57 (d, J = 8.1 Hz, 1H), 7.92 – 7.88 (m, 3H), 7.73 (d, J = 8.2 Hz, 1H), 7.67 (dt, J = 7.3, 3.8 Hz, 1H), 7.48 (dd, J = 15.4, 8.2 Hz, 1H), 6.99 (td, J = 8.5, 2.0 Hz, 1H).

Example 1b – synthesis of compound 76 (BC18703)



General Procedure for the Preparation of Compound 3:

To a solution of **1** (0.5 g, 2.51 mmol, 1 eq) in *i*-PrOH (15 mL) was added **2** (367 mg, 2.76 mmol, 1.1 eq) and DIEA (650 mg, 5.02 mmol, 2 eq). The reaction was stirred at 85 °C overnight. The solution was concentrated and the residue was purified by silica column chromatography (PE/EA, 2:1) to give 0.45 g **3** (yellow oil, 61%). MS (ESI) m/z : 296 $[M+H]^+$

General Procedure for the Preparation of Compound 5

To a solution of **3** (0.4 g, 1.36 mmol, 1 eq) in dioxane/H₂O (2:1, 1.5 mL) was

added **4** (632 mg, 2.04 mmol, 1.5 eq), K₂CO₃ (844 mg, 6.12 mmol, 4.5 eq) and PdCl₂(dppf) (95 mg, 0.13 mmol, 0.1 eq) under N₂. The mixture was stirred at 85 °C overnight. The mixture was filtered and the filter cake was washed by EA. The organic phase was washed by brine, then dried and concentrated. The residue was purified by silica column chromatography (PE/EA, 5:1) to give 0.4 g **5** (yellow solid, 70%). MS (ESI) m/z: 443[M+H]⁺.

General Procedure for the Preparation of Compound 6

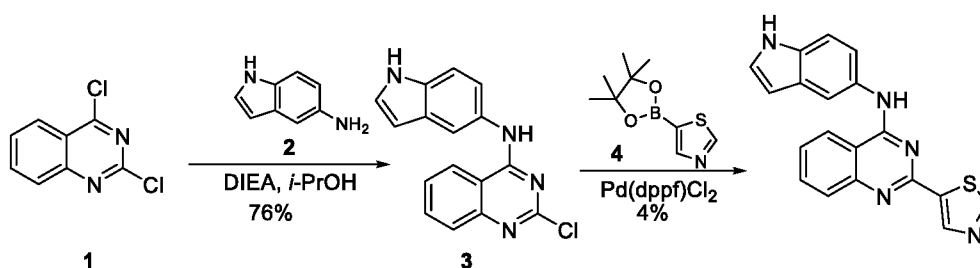
To a solution of **5** (0.2 g, 0.45 mmol, 1 eq) in MeOH (5 mL) was added Pd(OH)₂ (30 mg, 15% W/W) under N₂. The system was evacuated and backfilled with H₂ three times. After stirred at rt overnight, the mixture was filtered and the filtrate was concentrated to give 0.16 g **6** (colorless oil, 80%). MS (ESI) m/z: 445[M+H]⁺.

General Procedure for the Preparation of Compound BC18703

To a solution of **6** (160 mg) in MeOH (2 mL) was added 3M HCl/EA (4 mL). After stirred at rt for 2 h, the solution was concentrated to give 120 mg of **BC18703** (gray solid, 88%). MS (ESI) m/z: 345[M+H]⁺, 343[M-H]⁻.

¹H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 9.13 (d, J = 11.3 Hz, 1H), 8.96 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 8.14 (s, 1H), 8.07 – 8.03 (m, 2H), 7.79 (ddd, J = 8.2, 5.3, 2.6 Hz, 1H), 7.75 (dd, J = 9.0, 1.6 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 3.36 – 3.33 (m, 1H), 3.29 (d, J = 11.7 Hz, 2H), 2.94 (dd, J = 21.0, 11.0 Hz, 2H), 2.11 (d, J = 13.0 Hz, 2H), 2.05 – 1.92 (m, 2H).

Example 1c - synthesis of compound 78 (BC18705)

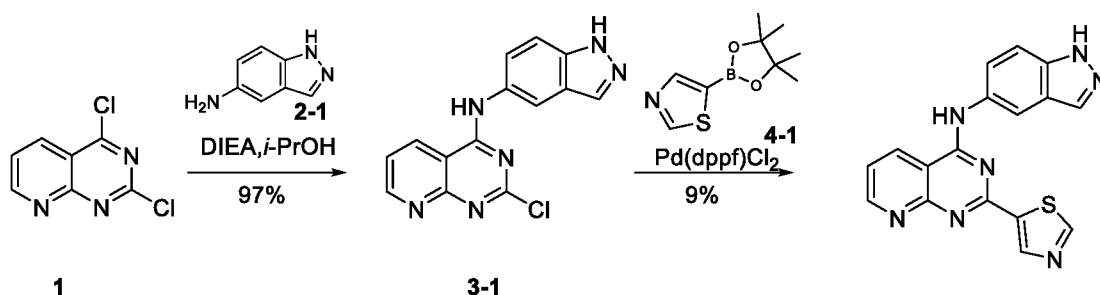


General Procedure for the Preparation of Compound 3

To a solution of **1** (200 mg, 1.0 mmol, 1 eq) in *i*-PrOH (3 mL) was added DIEA (284 mg, 2.0 mmol, 2 eq) and **2** (146 mg, 1.1 mmol, 1.1 eq). The reaction was stirred at 85 °C overnight. The solution was concentrated and the residue was purified by silica column chromatography (PE/EA, 2:1) to give 150 mg **3** (yellow solid, 76%). MS (ESI) m/z: 295 [M+H]⁺.

General Procedure for the Preparation of Compound BC18705

To a solution of **3** (100 mg, 0.339 mmol, 1 eq) in dioxane/H₂O (1:1, 3 mL) was added **4** (215 mg, 1.02 mmol, 3 eq), K₂CO₃ (210 mg, 1.5 mmol, 4.5 eq) and Pd(dppf)Cl₂ (25 mg, 0.034 mmol, 0.1 eq) under N₂. The mixture was stirred at 95 °C overnight. The mixture was concentrated and the residue was purified by Prep-HPLC to give 5 mg **BC18705** (off-white solid, 4%). MS (ESI) m/z: 344[M+H]⁺, 342[M-H]⁻. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.88 (s, 1H), 9.11 (s, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.45 (s, 1H), 8.03 (s, 1H), 7.88 – 7.69 (m, 2H), 7.62 – 7.47 (m, 20H), 7.43 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 2.7 Hz, 1H), 6.46 (s, 1H).

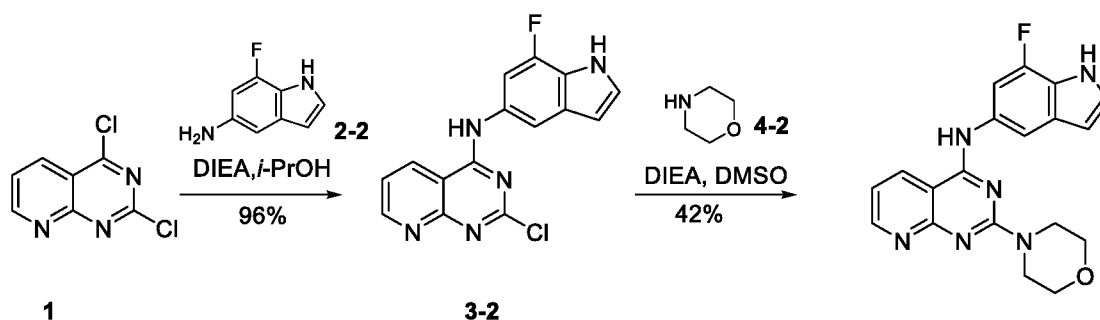
Example 1d – synthesis of compound 383 (BC18829)*General Procedure for the Preparation of Compound 3-1*

To a solution of **1** (0.2 g, 1.01 mmol, 1 eq) in *i*-PrOH (3 mL) was added **2** (148 mg, 1.11 mmol, 1.1 eq) and DIEA (260 mg, 2.02 mmol, 2 eq). The reaction was stirred at 85 °C overnight. The reaction was filtered. The cake was dried to give 0.29 g **3-1** (yellow solid, 97%). MS (ESI) m/z: 297 [M+H]⁺.

General Procedure for the Preparation of BC18829

To a solution of **3-1** (50 mg, 0.17 mmol, 1 eq) in dioxane/H₂O (4:1, 5 mL) was added **4-1** (40 mg, 0.19 mmol, 1.1 eq), K₂CO₃ (47 mg, 0.34 mmol, 2 eq) and PdCl₂(dppf) (25 mg, 0.03 mmol, 0.2 eq) under N₂. The mixture was stirred at 95 °C for 4 h. The mixture was filtered. The filter cake was washed by EA and the organic phase was dried and concentrated. The residue was purified by Prep-TLC (DCM/MeOH, 10:1) to give 5 mg **BC18829** (brown solid, 9%). MS (ESI) m/z: 346[M+H]⁺, 344[M-H]⁻.

¹H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 9.37 – 9.15 (m, 2H), 9.06 (s, 1H), 8.63 (dd, J = 7.1, 5.9 Hz, 1H), 8.37 – 8.05 (m, 2H), 7.89 – 7.48 (m, 3H).

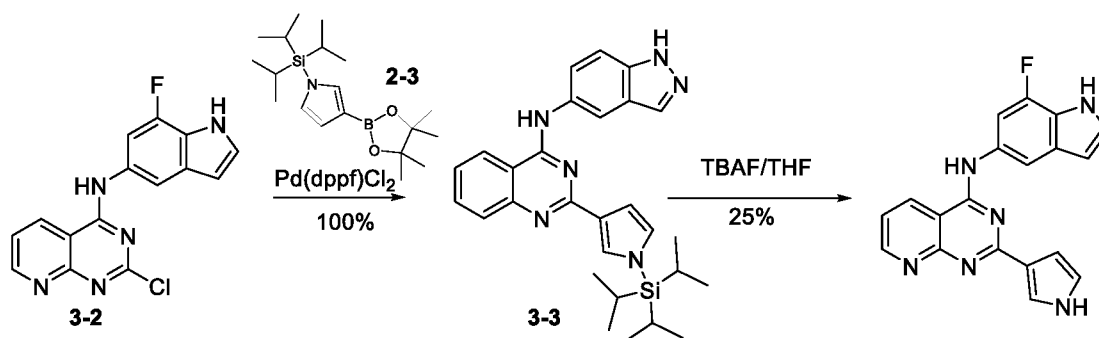
Example 1e – Synthesis of compound 384 (BC18830)*General Procedure for the Preparation of Compound 3-2*

To a solution of **1** (0.2 g, 1.01 mmol, 1 eq) in *i*-PrOH (3 mL) was added **2** (167 mg, 1.11 mmol, 1.1 eq) and DIEA (260 mg, 2.02 mmol, 2 eq). The reaction was stirred at 85 °C overnight. The reaction was filtered. The cake was dried to give 0.3 g **3-2** (yellow solid, 96%). MS (ESI) *m/z*: 314 [M+H]⁺

General Procedure for the Preparation of BC18830

To a solution of **3-2** (0.1 g, 0.32 mmol, 1 eq) in DMSO (5 mL) was added **4-2** (34 mg, 0.38 mmol, 1.2 eq) and DIEA (83 mg, 0.64 mmol, 2 eq). The reaction was stirred at 95 °C for 2 h and quenched with H₂O (5 mL). The mixture was extracted with EA (10 mL×2). The organic phase was dried and concentrated. The residue was purified by Prep-TLC to give 49 mg BC18830 (yellow solid, 42%). MS (ESI) *m/z*: 365[M+H]⁺, 363[M-H]⁻.

¹H NMR (400 MHz, DMSO) δ 11.59 (s, 1H), 9.86 (s, 1H), 8.77 – 8.60 (m, 2H), 7.66 (s, 1H), 7.47 – 7.28 (m, 2H), 7.23 – 7.11 (m, 1H), 6.50 (s, 1H), 3.73 (brs, 4H), 3.62 (d, *J* = 3.7 Hz, 7H).

Example 1f – synthesis of compound 385 (BC18831)*General Procedure for the Preparation of 3-3*

To a solution of **3-2** (as prepared in Example 1e) (150 mg, 0.48 mmol, 1 eq) in dioxane/H₂O (4:1, 5 mL) was added **2-3** (185 mg, 0.53 mmol, 1.1 eq), K₂CO₃ (133

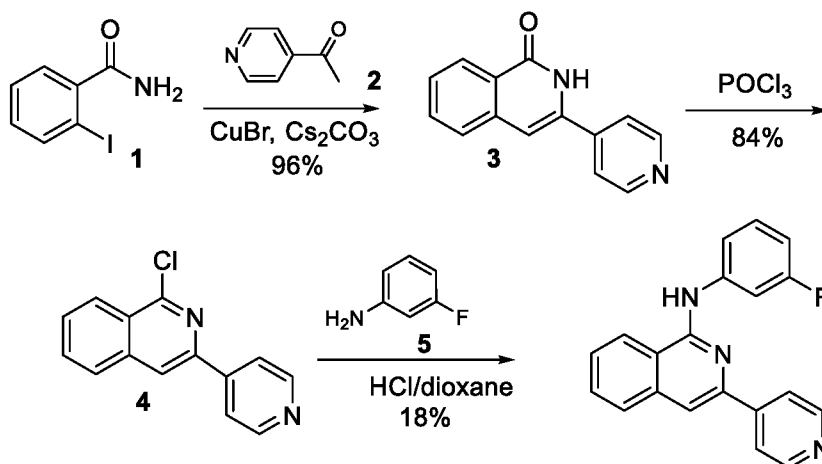
mg, 0.96 mmol, 2 eq) and Pd(dppf)Cl₂ (37 mg, 0.05 mmol, 0.1 eq) under N₂. The mixture was stirred at 95 °C for 4 h. The mixture was filtered. The filter cake was washed by EA and the organic phase was dried and concentrated to give 245 mg **3-3** (yellow solid, 100%). MS (ESI) m/z: 483[M+H]⁺

General Procedure for the Preparation of Compound BC18831

To a solution of **3-3** (245 mg crude, 0.51 mmol, 1 eq) in THF (2 mL) was added 1 M TBAF in THF (1.02 mL, 1.02 mmol 2 eq). The reaction was stirred at rt for 4 h. The mixture was concentrated and the residue was purified by Prep-HPLC to give 44 mg **BC18831** (yellow solid, 25%). MS (ESI) m/z: 345[M+H]⁺, 343[M-H]⁻

¹H NMR (400 MHz, DMSO) δ 11.58 (s, 1H), 11.18 (s, 1H), 9.83 (s, 1H), 8.88 (dd, J = 15.9, 5.5 Hz, 2H), 8.13 (s, 1H), 7.92 (s, 1H), 7.66 (d, J = 13.9 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H), 7.47 – 7.37 (m, 2H), 6.82 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 1.3 Hz, 1H), 6.57 – 6.50 (m, 1H).

Example 1g –synthesis of compound 43 (BC18663)



General Procedure for the Preparation of Compound 3

To a solution of **1** (1.5 g, 6.1 mmol, 1 eq) in DMSO (6 mL) was added **2** (1.1 g, 9.1 mmol, 1.5 eq), cesium carbonate (4.0 g, 12.2 mol, 2.0 eq) and copper (I) bromide (86 mg, 0.6 mmol, 0.1 eq). The mixture was stirred at 80 °C for 4 h. The mixture was diluted with water (30 mL). The solid precipitated was collected and dried to give 1.3 g **3** (grey solid, 96%). MS (ESI) m/z: 223 [M+H]⁺

General Procedure for the Preparation of Compound 4

To a solution of compound **3** (220 mg, 1.0 mmol, 1 eq) in DMSO (0.6 mL) was added phosphorus oxychloride (465 mL, 5.0 mmol, 5 eq). The mixture was stirred at 80 °C for 3.5 h. After completion, the mixture was poured into ice (~1 g).

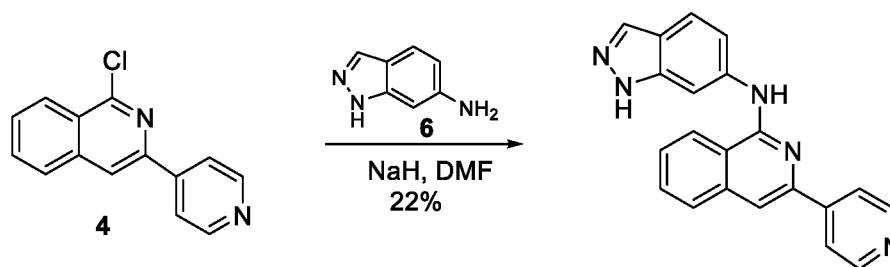
The solid was collected and dried to give 200 mg **4** (yellow solid, 84%). MS (ESI) m/z: 241[M+H]⁺

General Procedure for the Preparation of Compound BC18663

To a solution of **4** (83 mg, 0.35 mmol, 1.0 eq) in 4 M HCl/dioxane (2 mL) was added **5** (58 mg, 0.53 mmol, 1.5 eq). The reaction was stirred at 92 °C for 96 h. The solution was concentrated and the residue was purified by Prep-HPLC to give 19 mg **BC18663** (yellow solid, 18%). MS (ESI) m/z: 316[M+H]⁺, 314[M-H]⁻

¹H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 8.67 (dd, J = 4.6, 1.6 Hz, 2H), 8.56 (d, J = 8.7 Hz, 1H), 8.05 (dd, J = 4.5, 1.7 Hz, 3H), 8.00 – 7.91 (m, 2H), 7.83 – 7.72 (m, 2H), 7.68 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.39 (dd, J = 15.3, 8.2 Hz, 1H), 6.82 (td, J = 8.1, 1.9 Hz, 1H).

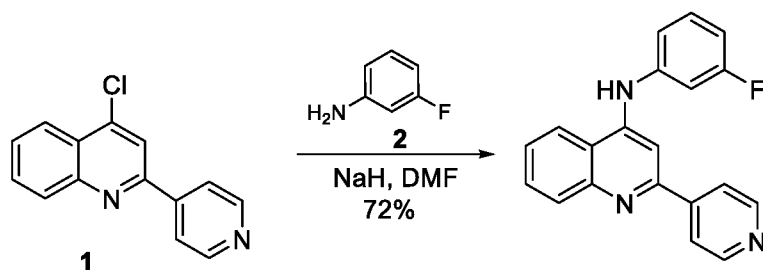
Example 1h – synthesis of compound 48 (BC18668)



General Procedure for the Preparation of BC18668

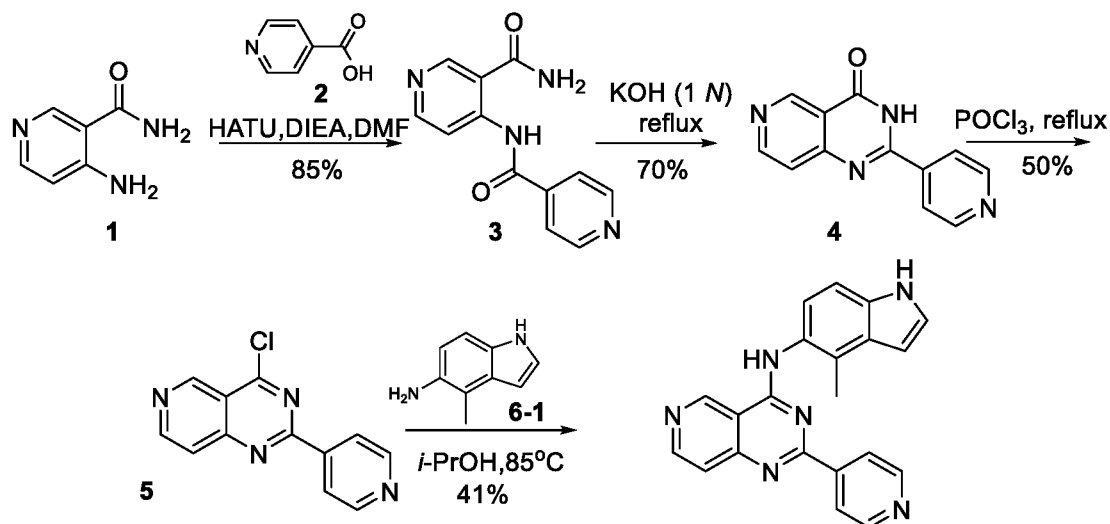
To a solution of **6** (57 mg, 0.43 mmol, 1 eq) in DMF (2 mL) was added 60% NaH (52 mg, 1.29 mmol, 3 eq) at 0 °C. The mixture was stirred for 10 min and then **4** (as prepared in Example 1g) (103 mg, 0.43 mmol, 1 eq) was added in. The mixture was stirred at 80 °C for 3 hours. Water (10 mL) was added in. The solid precipitated was collected and purified by Prep-HPLC to give 31 mg **BC18668** (white solid, 22%). MS (ESI) m/z: 338[M+H]⁺

¹H NMR (400 MHz, DMSO) δ 8.73 (d, J = 6.1 Hz, 2H), 8.70 – 8.63 (m, 2H), 8.23 – 8.17 (m, 4H), 8.15 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.5 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.22 (s, 1H), 6.67 (dd, J = 8.6, 1.7 Hz, 1H), 5.60 (s, 2H).

Example 1i – Synthesis of compound 69 (BC18689)*General Procedure for the Preparation of Compound BC18689*

To a solution of **2** (111 mg, 1.0 mmol, 1.2 eq) in DMF (4 mL) was added 60% NaH (100 mg, 2.49 mmol, 3 eq) at 0 °C and the mixture was stirred for 15 min, then **1** (prepared by the same literature, 0.2 g, 0.83 mmol, 1 eq) was added into the above solution. The mixture was heated to 80 °C for 3 h. After cooled to rt, H₂O (5 mL) was added slowly. The mixture was extracted by EA (10 mL×2) and the organic phase was concentrated. The residue was purified by Prep-TLC to give 187 mg **BC18689** (white solid, 72%). MS (ESI) m/z: 316 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 9.25 (s, 1H), 8.67 (dd, J = 4.5, 1.6 Hz, 2H), 8.37 (dd, J = 8.2, 0.8 Hz, 1H), 8.01 – 7.96 (m, 3H), 7.76 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.61 (s, 1H), 7.58 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.29 (dd, J = 7.7, 2.3 Hz, 1H), 7.24 (dt, J = 11.1, 2.3 Hz, 1H), 6.93 (td, J = 8.5, 2.4 Hz, 1H).

Example 1j – Synthesis of compound 126 (BC18763)*General Procedure for the Preparation of Compound 3*

To a solution of **1** (7.7 g, 56 mmol, 1.0 eq) in DMF (80 mL) was added **2** (8.2 g, 67.2 mmol, 1.2 eq), HATU (27.6 g, 73 mmol, 1.3 eq) and DIEA (14.4 g, 112 mmol,

2.0 eq) under N₂. The reaction was stirred at rt overnight. The reaction mixture was concentrated and the residue was purified by silica column chromatography (DCM/MeOH, 50:1) to give 11.5 g **3** (yellow solid, 85%). MS (ESI) m/z: 243 [M+H]⁺

General Procedure for the Preparation of Compound 4

A solution of **3** (2 g, 8.26 mmol, 1.0 eq) in KOH (1N, 20 mL) was heated to 100°C and stirred for 3 h. TLC showed no **3** left. The mixture was adjusted to pH 7 with aq HCl (4 M). The mixture was filtered. The solid precipitated was collected and dried to give 1.4 g **4** (white solid, 70%). MS (ESI) m/z: 225 [M+H]⁺

General Procedure for the Preparation of Compound 5

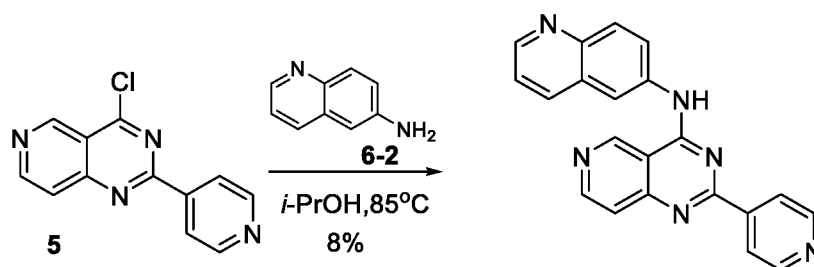
A solution of **4** (1.4 g, 6.3 mmol, 1.0 eq) in POCl₃ (10 mL) was stirred at 100°C overnight. The reaction was concentrated and the residue was adjusted pH to 9~10 with saturated Na₂CO₃. The mixture was extracted with CHCl₃ (15 mL×3) and the organic phase was dried and concentrated to give 750 mg **5** (yellow solid, 50%). MS (ESI) m/z: 243 [M+H]⁺

General Procedure for the Preparation of BC18763

To a solution of **5** (50 mg, 0.21 mmol, 1 eq) in *i*-PrOH (3 mL) was added **6-1** (33 mg, 0.23 mmol, 1.1 eq). The reaction was stirred at 85 °C overnight. The reaction mixture was filtered. The cake was washed by *i*-PrOH and dried to give 30.1 mg **BC18763** (brown solid, 41%). MS (ESI) m/z: 353 [M+H]⁺, 351 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 11.26 (s, 1H), 10.81 (s, 1H), 10.05 (s, 1H), 8.80 (d, J = 37.3 Hz, 3H), 8.18 (s, 2H), 7.84 (d, J = 5.4 Hz, 1H), 7.51 – 7.25 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 6.55 (s, 1H), 2.47 (s, 3H)

Example 1k – synthesis of compound 127 (BC18764)



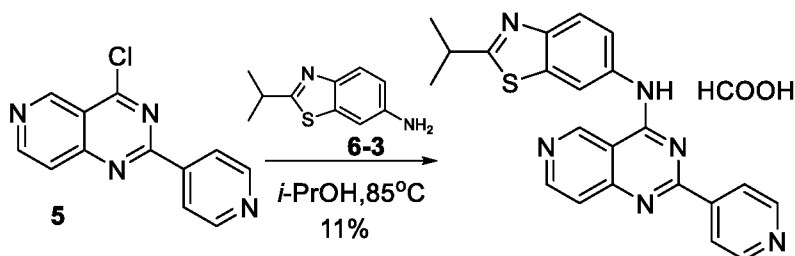
General Procedure for the Preparation of BC18764

To a solution of **5** (as prepared in Example 1j) (100 mg, 0.21 mmol, 1 eq) in *i*-PrOH (3 mL) was added **6-2** (33 mg, 0.23 mmol, 1.1 eq). The reaction was stirred at 85 °C overnight. The reaction mixture was concentrated and the residue was purified

with Prep-HPLC to give 10.6 mg **BC18764** (brown solid, 8%). MS (ESI) m/z: 351 [M+H]⁺, 349 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.95 (s, 1H), 8.85 (d, J = 5.7 Hz, 2H), 8.76 (d, J = 5.9 Hz, 2H), 8.55 (d, J = 2.0 Hz, 1H), 8.42 (d, J = 7.6 Hz, 1H), 8.27 (dd, J = 5.4, 3.7 Hz, 3H), 8.11 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 5.9 Hz, 1H), 7.55 (dd, J = 8.1, 4.2 Hz, 1H).

Example 1l – synthesis of compound 120 (BC18757)

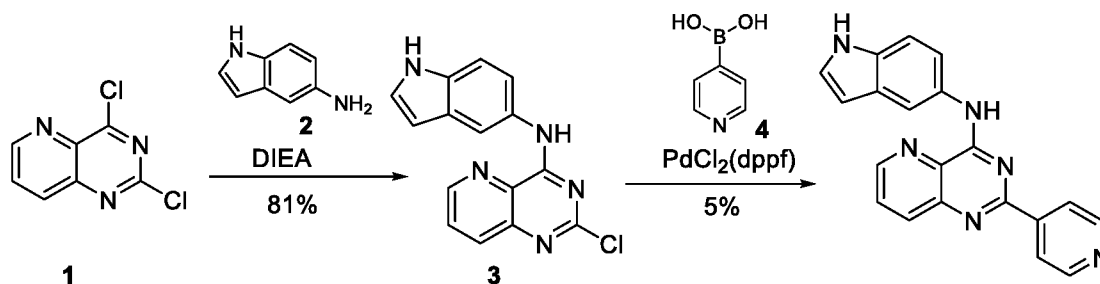


General Procedure for the Preparation of BC18757

To a solution of **5** (as prepared in Example 1j) (100 mg, 0.41 mmol, 1 eq) in *i*-PrOH (3 mL) was added **6-3** (86 mg, 0.45 mmol, 1.1 eq). The reaction was stirred at 85 °C overnight. The reaction mixture was concentrated and the residue was purified with Prep-HPLC to give 20 mg **BC18757** (yellow solid, 11%). MS (ESI) m/z: 399 [M+H]⁺, 397 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 10.67 (s, 1H), 9.84 (s, 1H), 8.80 (d, J = 5.8 Hz, 1H), 8.69 (d, J = 5.5 Hz, 2H), 8.52 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 5.8 Hz, 2H), 7.99 (d, J = 8.7 Hz, 1H), 7.89 (dd, J = 8.8, 1.9 Hz, 1H), 7.70 (d, J = 5.7 Hz, 1H), 4.26 (s, 1H), 1.40 (d, J = 6.9 Hz, 6H).

Example 1m – synthesis of compound 83 (BC18711)



General Procedure for the Preparation of Compound 3

To a solution of **1** (1.0 g, 5.0 mmol, 1 eq) in *i*-PrOH (15 mL) was added **2** (726 mg, 5.5 mmol, 1.1 eq) and DIEA (1.29 g, 10.0 mmol, 2 eq). The reaction was stirred

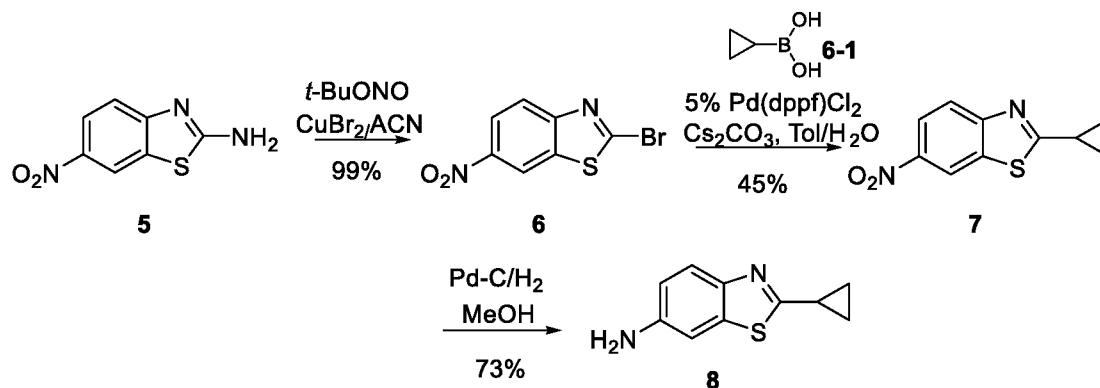
at 85 °C for 4 h. The mixture was filtered. The cake was washed by *i*-PrOH and dried to give 1.2 g **3** (yellow solid, 81%). MS (ESI) *m/z*: 296 [M+H]⁺

General Procedure for the Preparation of BC18711

To a solution of **3** (700 mg, 2.36 mmol, 1 eq) in dioxane/H₂O (4:1, 10 mL) was added **4** (348 mg, 2.83 mmol, 1.2 eq), K₂CO₃ (651 mg, 4.72 mmol, 2 eq) and PdCl₂(dppf) (176 mg, 0.24 mmol, 0.1 eq) under N₂. The mixture was stirred at 119 °C overnight. The mixture was filtered. The filter cake was washed by EA and the organic phase was dried and concentrated. The residue was purified by Prep-HPLC to give 34 mg **BC18711** (gray solid, 5%). MS (ESI) *m/z*: 339[M+H]⁺, 337[M-H]⁻

¹H NMR (400 MHz, DMSO) δ 12.33 (s, 1H), 11.43 (s, 1H), 10.09 (dd, *J* = 4.2, 1.4 Hz, 1H), 9.92 (d, *J* = 5.4 Hz, 2H), 9.44 (ddd, *J* = 11.0, 6.8, 1.8 Hz, 4H), 9.09 (dd, *J* = 8.5, 4.2 Hz, 1H), 8.89 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.65 (d, *J* = 8.7 Hz, 1H), 8.56 (t, *J* = 2.7 Hz, 1H), 7.68 (s, 1H).

Example 1n – synthesis of intermediate 8 (useful in making compound BC18847)



General Procedure for the Preparation of Compound 6

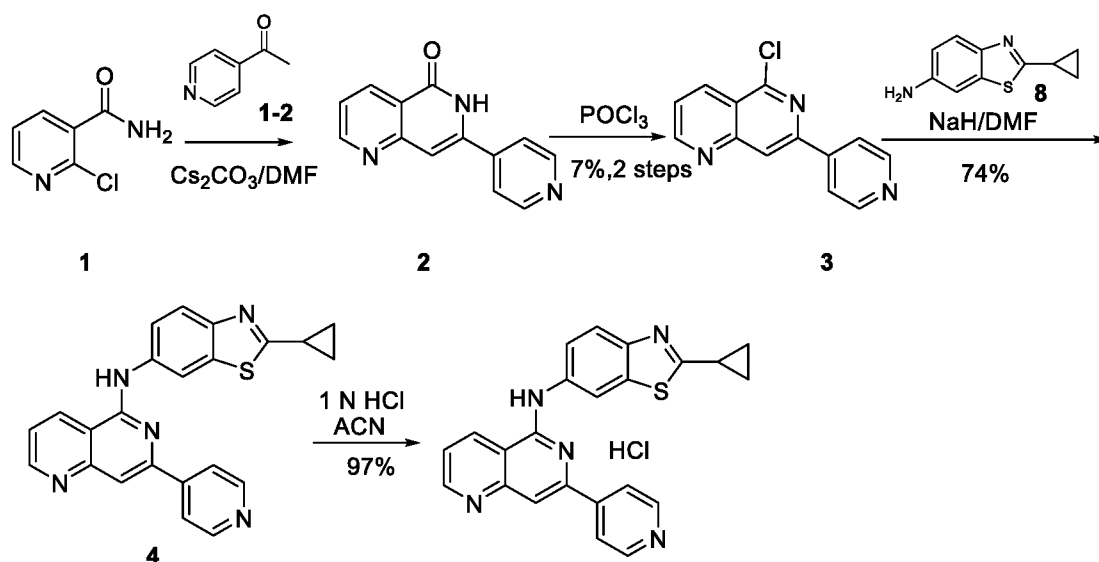
Compound **5** (44 g, 225 mmol, 1 eq), *tert*-butyl nitrite (45 mL, 375 mmol, 1.67 eq) and CuBr₂ (60 g, 270 mmol, 1.2 eq) was suspended in acetonitrile (500 mL, 10V) and stirred at room temperature for 1-2 hour. The progress of the reaction was monitored by TLC (PE: EA 5:1). The resulting reaction mixture was quenched with 1 N HCl aqueous solution (3 L) and extracted with CH₂Cl₂ (3×2 L). The combined organic layers were dried over Na₂SO₄, and concentrated to give compound **6** (66.4 g, 99%) as yellow powder, which was used for next step without further purification. MS (ESI) *m/z*: 259[M+H]⁺.

General Procedure for the Preparation of Compound 7

To a solution of **6** (50.0 g, 194 mmol, 1.0 eq) in toluene/H₂O (V/V=2:1, 2 L) was added **6-1** (50 g, 581 mmol, 3.0 eq), Cs₂CO₃ (126 g, 389 mmol, 2.0 eq) and Pd(dppf)Cl₂ (14.2 g, 19.4 mmol, 0.1 eq). The mixture was evacuated and backfilled with Ar three times and then stirred at 100 °C overnight. The mixture was filtered through a pad of Celite, and washed with ethyl acetate (mL). The organic layers were washed with water and brine and dried over sodium sulfate. Concentrated and the residue was purified by silica column chromatography (PE/EA, 10:1) to give 19.1 g **7** (off-white solid, 45%).

General Procedure for the Preparation of Compound 8

To a solution of compound **7** (20.0 g, 90.9 mmol, 1.0 eq) in MeOH (200 mL) was added 10% Pd-C (6 g, 20% W/W) and stirred under H₂ at r.t for 3~4 h. TLC showed **7** left, another batch of Pd-C (6 g, 20% W/W) was added and the reaction was continued to stir at r.t for 4~6 h. TLC showed no **7** left but there was two spots on TLC. Another batch of Pd-C (6 g, 20% W/W) was added and the reaction was continued to stir at r.t for 3~5 h. The progress of the reaction was monitored by HPLC. After TLC showed only one spot, the mixture was filtered through Celite, washed with methanol (50 mL), and the filtrate was concentrated to give the crude which was recrystallized by EA to give 12.1 g **8** (gray solid, 73%). MS (ESI) m/z: 191[M+H]⁺

Example 1o – synthesis of compound 241 (BC18847)

General Procedure for the Preparation of Compound 2

Compound **1** (150.0 g, 960 mmol, 1.0 eq), 1-(pyridin-4-yl)ethanone (174.0 g, 1.44 mol, 1.5 eq), cesium carbonate (630 g, 1.93 mol, 2.0 eq) and copper(I) bromide (13.8 g, 9.6 mmol, 0.1 eq) was dissolved in N,N-dimethylformamide (750 mL) and stirred at 80 °C overnight, the mixture was diluted with water (2 L). The solid was filtered, washed with water, and dried to give a black residue (175.2 g) which was used for next step without further purification.

General Procedure for the Preparation of Compound 3

A solution of compound **2** (175.2 g) in phosphorus oxychloride (500 mL) was stirred at 110 °C overnight and the progress of the reaction checked by LCMS. Excess phosphorus oxychloride was distilled under reduced pressure. EA (400 mL) and water (200 mL) was added to the system. The mixture was adjusted to pH 7 with saturated aqueous NaHCO₃. The water phase was extracted with EA (500 mL×3). The organic phase was washed with brine and dried over anhydrous sodium sulfate, and concentrated to give a crude, which was purified by column chromatography on a silica gel (EA: PE= 10:1 to 1:1) to afford 14.5 g **3** (yellow solid, 7%, 2 steps). MS (ESI) m/z: 242[M+H]⁺

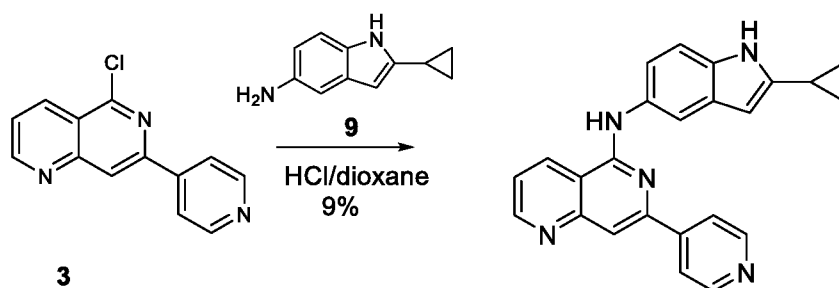
General Procedure for the Preparation of Compound 4

To a suspension of NaH (2.4 g, 100 mmol, 3eq) in DMF (65 mL) at 0 °C was added amine **8** (5.3 g, 33.7 mmol, 1.01 eq). The mixture was stirred at rt for 30 min. To above mixture was added compound **3** (8.0 g, 33.2 mmol, 1 eq). The mixture was stirred at 80 °C for 16 hours. After completion, the mixture was cooled to room temperature and water (350 mL) was added slowly. The solid collected was triturated with EA and dried to give 9.7 g **4** (yellow solid, 74%). MS (ESI) m/z: 396[M+H]⁺, 394[M-H]⁻

General Procedure for the Preparation of BC18847

To a solution of compound **4** (30 g, 75.9 mmol, 1 eq) in ACN (60 mL) was added 1N HCl (114 mL, 113.9 mmol, 1.5 eq.). The mixture was stirred for 0.5 h. Then the mixture was lyophilized to give 32 g **BC18847** (red solid, 97%). MS (ESI) m/z: 396[M+H]⁺, 394[M-H]⁻

¹H NMR (400 MHz, DMSO) δ 9.02 – 8.91 (m, 2H), 8.71 (d, *J* = 6.4 Hz, 2H), 8.37 (d, *J* = 6.5 Hz, 2H), 8.18 (d, *J* = 1.5 Hz, 1H), 7.90 (s, 1H), 7.73 – 7.62 (m, 3H), 2.47 (s, 1H), 1.30 – 1.15 (m, 2H), 1.09 – 0.94 (m, 2H).

Example 1p – synthesis of compound 244 (BC18850)*General Procedure for the Preparation of BC18850*

To a solution of **3** (as prepared in Example 1o) (0.12 g, 0.50 mmol, 1 eq) and **9** (0.17 g, 1.0 mmol, 2 eq) in NMP (1.5 mL) was added 4 M HCl/dioxane (0.13 mL, 0.50 mmol, 1 eq) and the mixture was stirred at 100 °C overnight. After cooled to rt, the mixture was purified by Prep-HPLC directly to give 17 mg **BC18850** (yellow solid, 9%). MS (ESI) m/z: 378[M+H]⁺.

¹H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 9.39 (s, 1H), 9.04 – 8.90 (m, 2H), 8.62 (dd, J = 4.6, 1.5 Hz, 2H), 8.05 (dd, J = 4.6, 1.6 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.59 (dd, J = 8.4, 4.3 Hz, 1H), 7.40 (dd, J = 8.6, 2.0 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.09 (d, J = 1.8 Hz, 1H), 1.99 (td, J = 8.4, 4.1 Hz, 1H), 0.98 – 0.89 (m, 2H), 0.82 – 0.74 (m, 2H).

Example 1 – Compound structures

The compounds in Table 1 were prepared as shown in the general scheme from readily available starting materials.

Table 1

No.	BC code	Structure
1	BC18607	
2	BC18608	

No.	BC code	Structure
3	BC18612	
4	BC18614	
5	BC18615	
6	BC18616	
7	BC18617	

No.	BC code	Structure
8	BC18618	
9	BC18619	
10	BC18625	
11	BC18626	
12	BC18627	
13	BC18628	

No.	BC code	Structure
14	BC18629	
15	BC18630	
16	BC18630 HCl salt	
17	BC18631	
18	BC18633	
19	BC18634	
20	BC18635	

No.	BC code	Structure
21	BC18636	
22	BC18637	
23	BC18639	
24	BC18640	
25	BC18641	
26	BC18642	

No.	BC code	Structure
27	BC18643	
28	BC18644	
29	BC18645	
30	BC18646	
31	BC18647	
32	BC18648	

No.	BC code	Structure
33	BC18649	
34	BC18652	
35	BC18653	
36	BC18654	
37	BC18655	
38	BC18656	
39	BC18657	

No.	BC code	Structure
40	BC18658	
41	BC18659	
42	BC18660	
43	BC18663	
44	BC18664	
45	BC18665	

No.	BC code	Structure
46	BC18666	
47	BC18667	
48	BC18668	
49	BC18669	
50	BC18670	
51	BC18671	

No.	BC code	Structure
52	BC18672	
53	BC18673	
54	BC18674	
55	BC18675	
56	BC18676	
57	BC18677	

No.	BC code	Structure
58	BC18678	
59	BC18679	
60	BC18680	
61	BC18681	
62	BC18682	
63	BC18683	

No.	BC code	Structure	No.	BC code	Structure
64	BC18684		70	BC18690	
65	BC18685		71	BC18693	
66	BC18686		72	BC18695	
67	BC18687		73	BC18697	
68	BC18688		74	BC18698	
69	BC18689		75	BC18702	

No.	BC code	Structure
76	BC18703	
77	BC18704	
78	BC18705	
79	BC18706	
80	BC18707	
81	BC18708	

No.	BC code	Structure
82	BC18709	
83	BC18711	
84	BC18713	
85	BC18714	
86	BC18717	
87	BC18718	

No.	BC code	Structure
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89	BC18722	
90	BC18724	
91	BC18725	
92	BC18726	
93	BC18727	
94	BC18728	

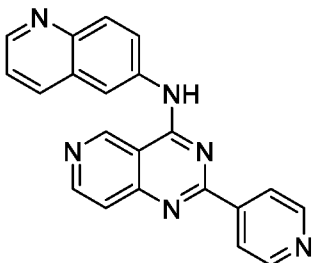
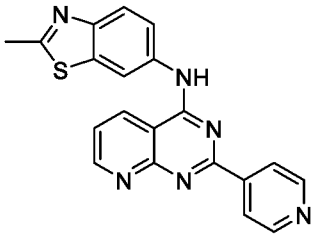
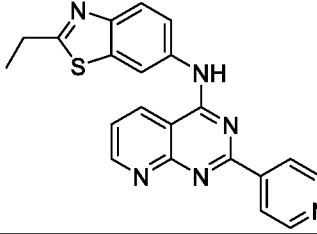
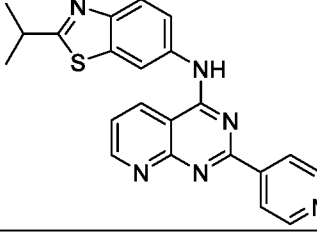
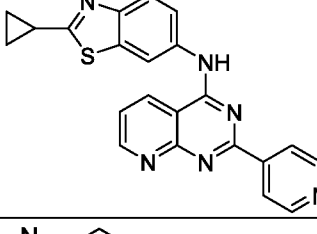
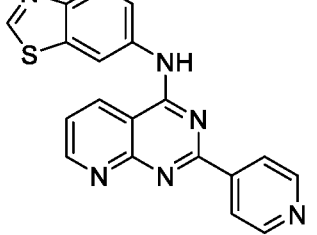
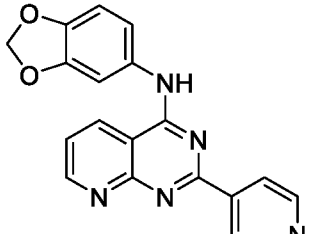
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96	BC18730	
97	BC18731	
98	BC18732	
99	BC18733	
100	BC18734	
101	BC18735	

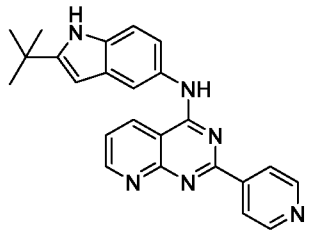
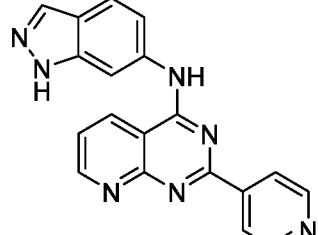
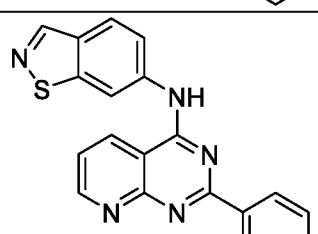
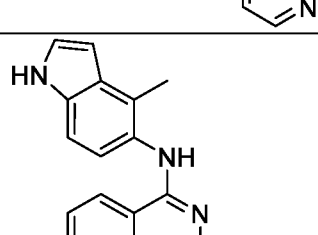
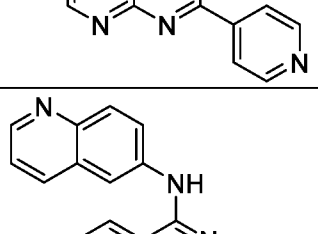
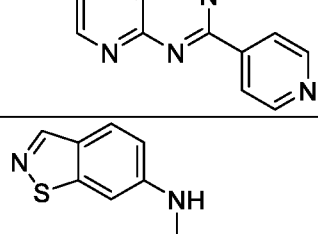
No.	BC code	Structure
102	BC18736	
103	BC18737	
104	BC18738	
105	BC18739	
106	BC18740	
107	BC18742	

No.	BC code	Structure
108	BC18743	
109	BC18744	
110	BC18745	
111	BC18746	
112	BC18747	
113	BC18748	

No.	BC code	Structure
114	BC18749	
115	BC18750	
116	BC18752	
117	BC18754	
118	BC18755	
119	BC18756	

No.	BC code	Structure
120	BC18757	
121	BC18758	
122	BC18759	
123	BC18760	
124	BC18761	
125	BC18762	
126	BC18763	

No.	BC code	Structure
127	BC18764	
128	BC18765	
129	BC18766	
130	BC18767	
131	BC18768	
132	BC18769	
133	BC18770	

No.	BC code	Structure
134	BC18771	
135	BC18772	
136	BC18773	
137	BC18774	
138	BC18775	
139	BC18776	

No.	BC code	Structure
140	BC18778	
141	BC18779	
142	BC18780	
143	BC18782	
144	BC18783	
145	BC18784	
146	BC18785	

No.	BC code	Structure
147	BC18786	
148	BC18787	
149	BC18788	
150	BC18789	
151	BC18790	
152	BC18791	
153	BC18792	

No.	BC code	Structure	No.	BC code	Structure
154	BC18793		157	BC18813	
155	BC18794		158	BC18815	
156	BC18816				

Note: Cmpd 35 was isolated and tested as TFA salt. Compounds 42, 51, 59, 63, 64, and 65 were each isolated and tested as HCl salt. Compounds 82, 83, 89, 106, 107, 108, 113, 115, 116, 117, 119, 120, and 121 were each isolated and tested as formate salt.

The following compounds shown in Table 1a may prepared using chemical routes that would be readily apparent to one of ordinary skill in the art from readily available starting materials.

Table 1a

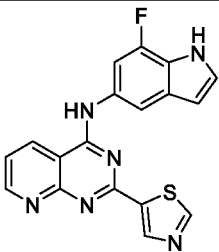
No.	BC. Code	Structure	No.	BC. Code	Structure
352	BC18795		353	BC18796	

No.	BC. Code	Structure	No.	BC. Code	Structure
354	BC18797		361	BC18804	
355	BC18798		362	BC18805	
356	BC18799		363	BC18806	
357	BC18800		364	BC18807	
358	BC18801		365	BC18808	
359	BC18802		366	BC18809	
360	BC18803		367	BC18810	

No.	BC. Code	Structure	No.	BC. Code	Structure
368	BC18811		375	BC18821	
369	BC18812		376	BC18822	
370	BC18814		377	BC18823	
371	BC18817		378	BC18824	
372	BC18818		379	BC18825	
373	BC18819		380	BC18826	
374	BC18820		381	BC18827	

No.	BC. Code	Structure
382	BC18828	
383	BC18829	
384	BC18830	
385	BC18831	
386	BC18832	
387	BC18833	
388	BC18834	

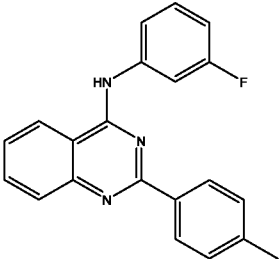
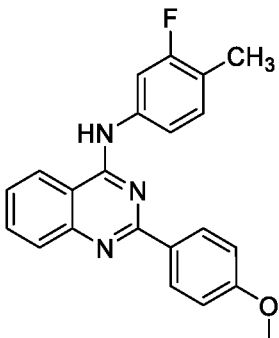
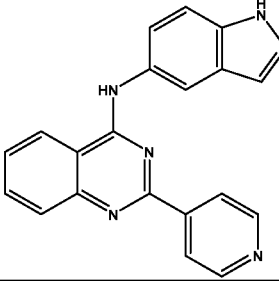
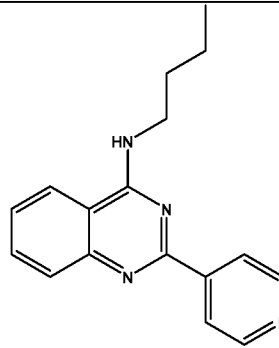
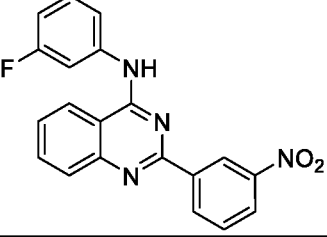
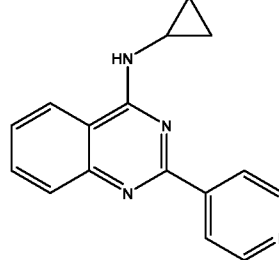
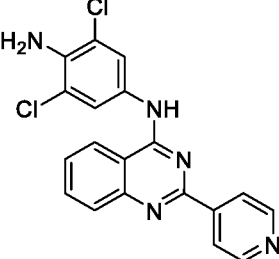
No.	BC. Code	Structure
389	BC18835	
390	BC18836	
391	BC18837	
392	BC18838	
393	BC18839	
394	BC18840	
395	BC18841	

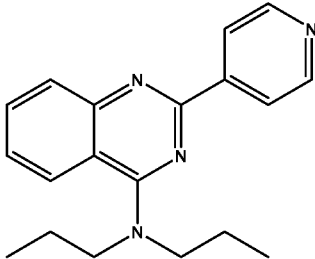
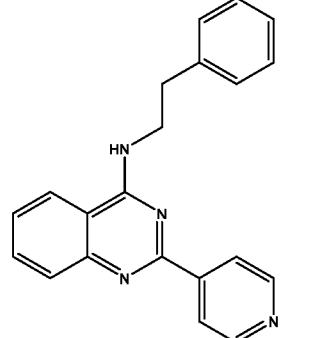
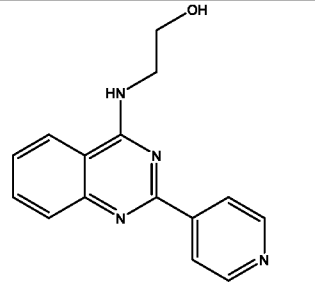
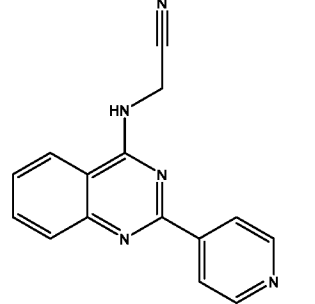
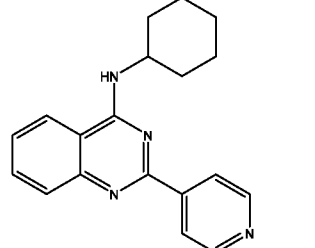
No.	BC. Code	Structure
396	BC18845	

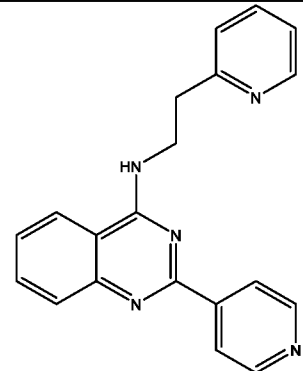
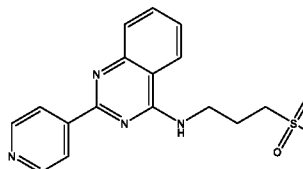
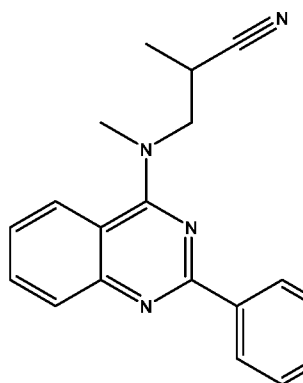
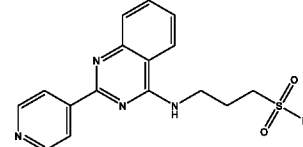
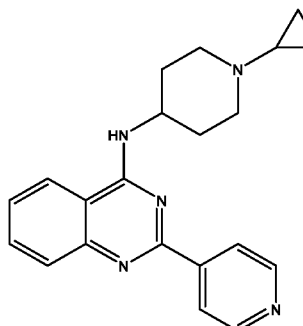
Note: Compounds 353, 364, and 376 were isolated and tested as HCOOH salts.

The following compounds (free base) provided in Table 2 were obtained from commercial sources (ChemDIV, Inc. and Molport, Inc.):

Table 2

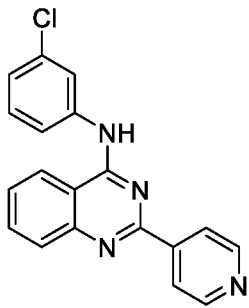
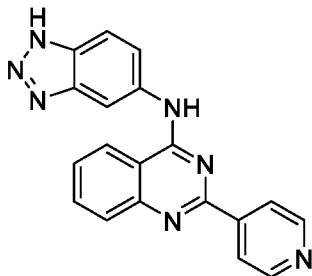
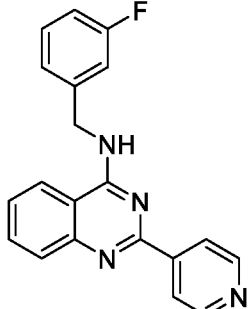
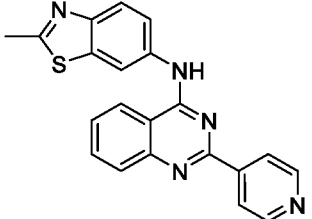
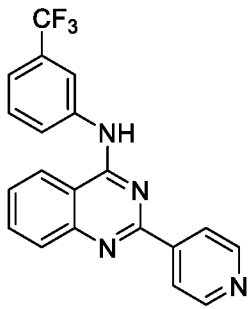
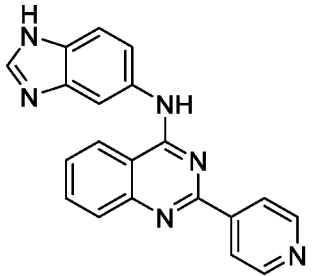
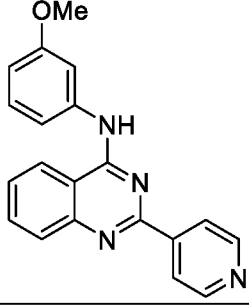
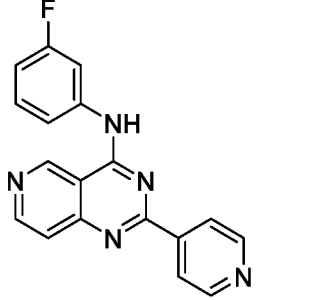
No.	BC code	Structure	No.	BC code	Structure
159	BC1820		163	BC18203	
160	BC18200		164	BC18204	
161	BC18201		165	BC18205	
162	BC18202				

No.	BC code	Structure
166	BC18206	
167	BC18207	
168	BC18208	
169	BC18209	
170	BC18210	

No.	BC code	Structure
171	BC18211	
172	BC18212	
173	BC18213	
174	BC18214	
175	BC18215	

No.	BC code	Structure
176	BC18216	
177	BC18217	
178	BC1834	
179	BC18601	
180	BC18602	

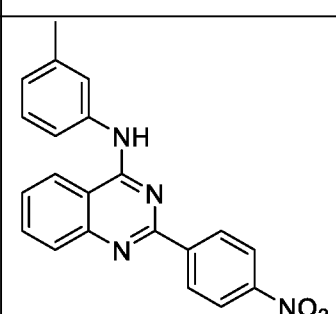
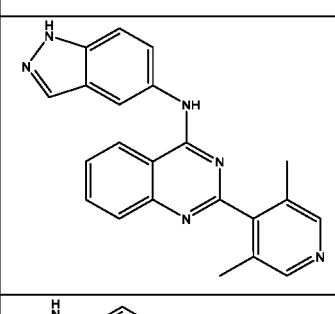
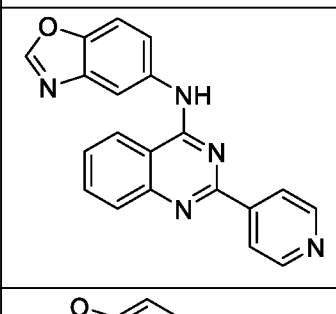
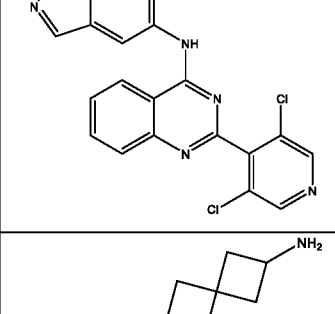
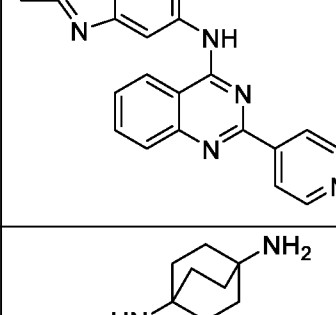
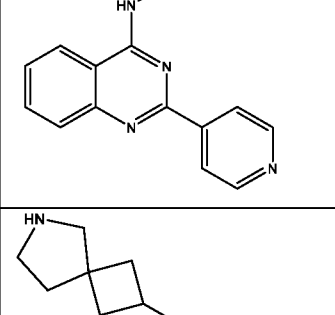
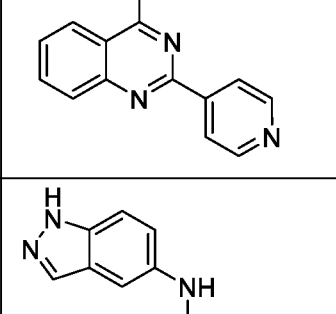
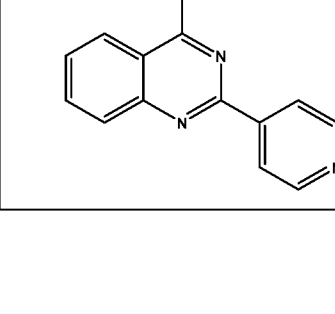
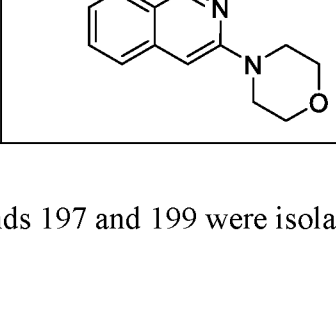
No.	BC code	Structure
181	BC18603	
182	BC18604	
183	BC18605	
184	BC18606	
185	BC18609	
186	BC18610	

No.	BC code	Structure	No.	BC code	Structure
187	BC18611		191	BC18632	
188	BC18613		192	BC18651	
189	BC18623		193	BC18661	
190	BC18624		194	BC18715	

The following compounds shown in Table 3 may prepared using chemical routes that would be readily apparent to one of ordinary skill in the art from readily available starting materials.

Table 3

No.	BC code	Structure	No.	BC code	Structure
195	BC1816		200	BC1839	
196	BC1835		201	BC1840	
197	BC1836		202	BC1841	
198	BC1837		203		
199	BC1838		204		

No.	BC code	Structure	No.	BC code	Structure
205			210		
206			211		
207			212		
208			213		
209					

Note: Compounds 197 and 199 were isolated and tested as HCl salts.

5

The following compounds shown in Table 4 were purchased from ChemDIV, Inc.

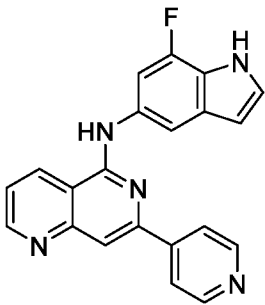
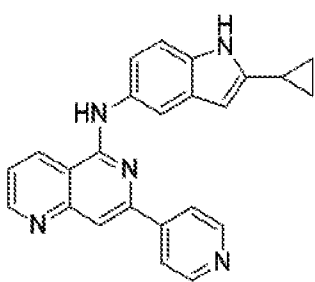
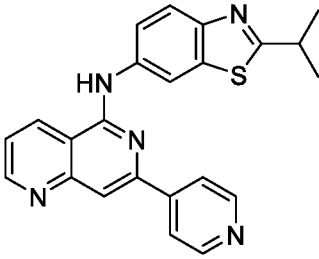
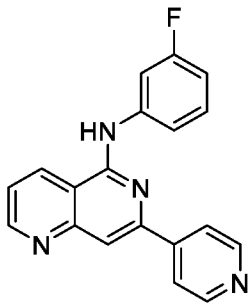
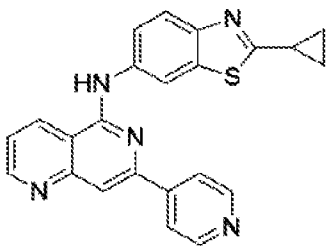
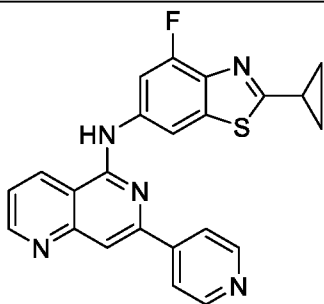
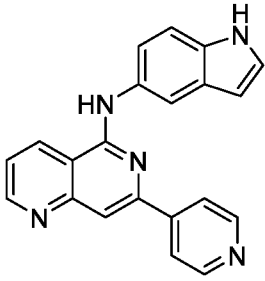
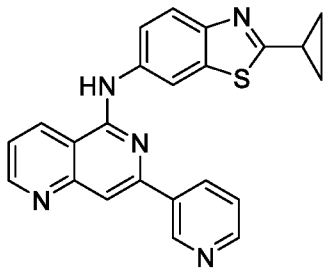
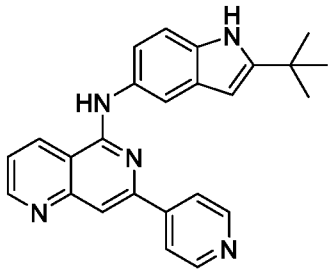
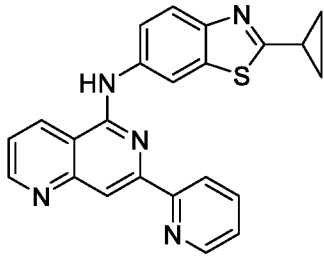
Table 4

No.	BC code	Structure	No.	BC code	Structure
214	BC1770		223	BC1780	
215	BC1771		224	BC1781	
216	BC1772		225	BC1782	
217	BC1773		226	BC1783	
218	BC1774		227	BC1784	
219	BC1775		228	BC1785	
220	BC1776				
221	BC1777				
222	BC1753				

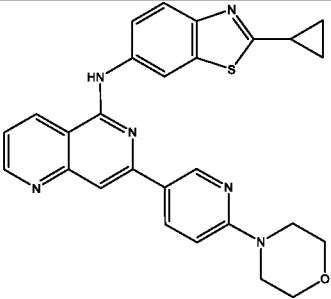
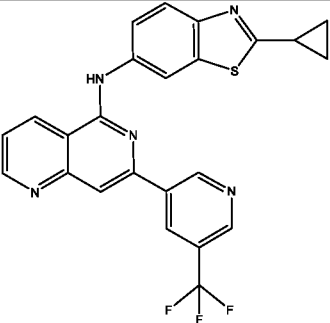
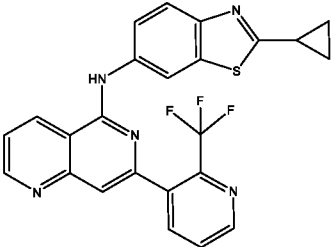
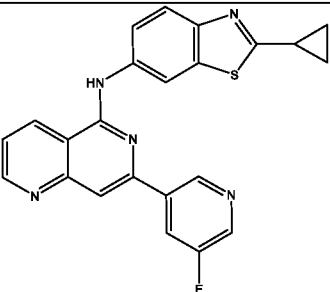
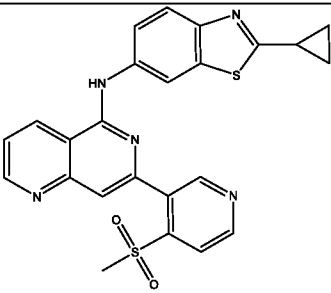
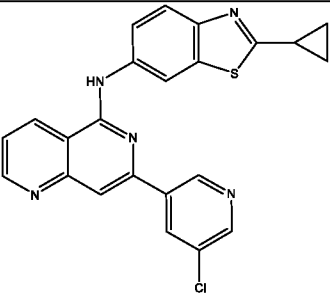
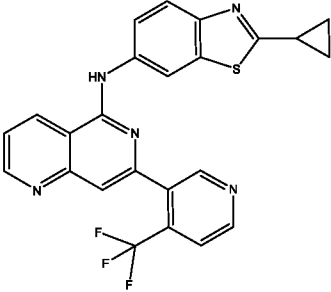
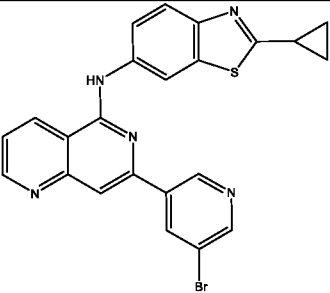
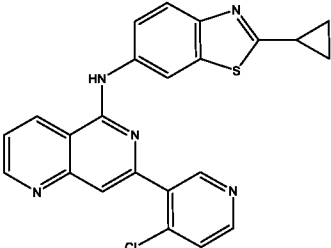
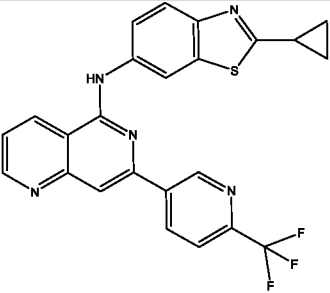
No.	BC code	Structure	No.	BC code	Structure
229	BC1786		233	BC1813	
230	BC1787		234	BC1814	
231	BC1811		235	BC1815	
232	BC1812		236	BC1817	
237	BC1818		238	BC1819	

The following compounds shown in Table 5 may be prepared using chemical routes that would be readily apparent to one of ordinary skill in the art from readily available starting materials.

Table 5

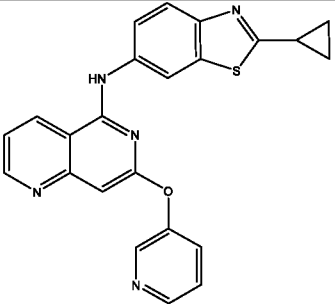
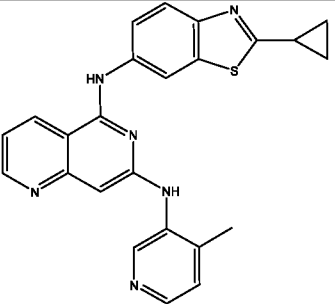
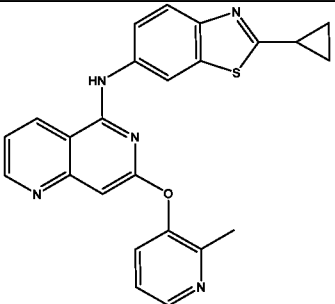
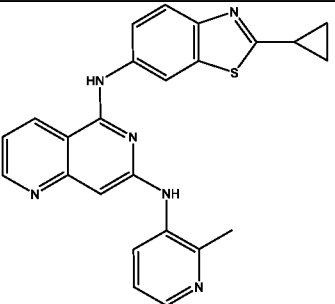
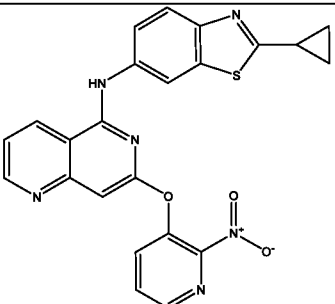
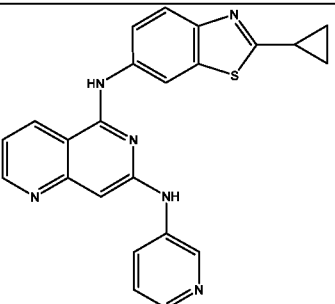
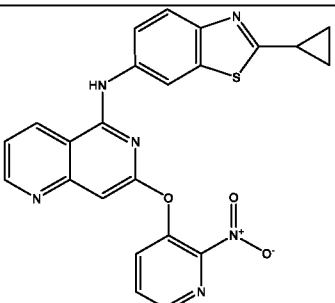
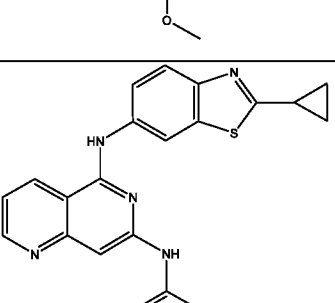
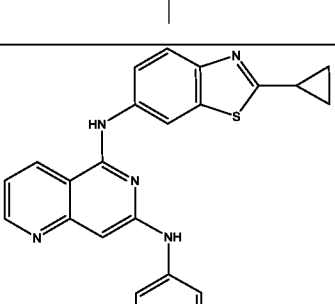
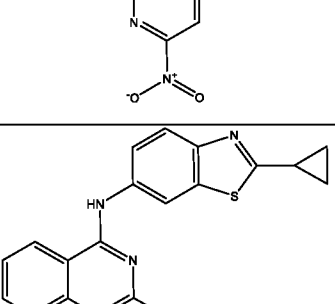
No.	BC code	Structure	No.	BC code	Structure
239	BC18842		244	BC18850	
240	BC18846		245	BC18851	
241	BC18847		246	BC18852	
242	BC18848		247	BC18853	
243	BC18849		248	BC18854	

No.	BC code	Structure	No.	BC code	Structure
249	BC191100		255	BC191106	
250	BC191101		256	BC191107	
251	BC191102		257	BC191108	
252	BC191103		258	BC191109	
253	BC191104		259	BC191110	
254	BC191105		260	BC191111	

No.	BC code	Structure	No.	BC code	Structure
261	BC191112		266	BC191117	
262	BC191113		267	BC191118	
263	BC191114		268	BC191119	
264	BC191115		269	BC191120	
265	BC191116		270	BC191121	

No.	BC code	Structure	No.	BC code	Structure
271	BC191122		276	BC191127	
272	BC191123		277	BC191128	
273	BC191124		278	BC191129	
274	BC191125		279	BC191130	
275	BC191126		280	BC191131	
			281	BC191132	

No.	BC code	Structure	No.	BC code	Structure
282	BC191133		288	BC191139	
283	BC191134		289	BC191140	
284	BC191135		290	BC191141	
285	BC191136		291	BC191142	
286	BC191137		292	BC191143	
287	BC191138				

No.	BC code	Structure	No.	BC code	Structure
293	BC191144		298	BC191149	
294	BC191145		299	BC191150	
295	BC191146		300	BC191151	
296	BC191147		301	BC191152	
297	BC191148		302	BC191153	

No.	BC code	Structure	No.	BC code	Structure
303	BC191154		308	BC191159	
304	BC191155		309	BC191160	
305	BC191156		310	BC191161	
306	BC191157		311	BC191162	
307	BC191158		312	BC191163	

No.	BC code	Structure	No.	BC code	Structure
313	BC191164		318	BC191169	
314	BC191165		319	BC191170	
315	BC191166		320	BC191171	
316	BC191167		321	BC191172	
317	BC191168		322	BC191173	

No.	BC code	Structure	No.	BC code	Structure
323	BC191174		329	BC191180	
324	BC191175		330	BC191181	
325	BC191176		331	BC191182	
326	BC191177		332	BC191183	
327	BC191178		333	BC191184	
328	BC191179		334	BC191185	

No.	BC code	Structure	No.	BC code	Structure
335	BC191186		341	BC191192	
336	BC191187		342	BC191193	
337	BC191188		343	BC191194	
338	BC191189		344	BC191195	
339	BC191190		345	BC191196	
340	BC191191		346	BC191197	

No.	BC code	Structure	No.	BC code	Structure
347	BC191198		350	BC191201	
348	BC191199		351	BC191202	
349	BC191200				

Note: Compounds 239, 240, 242, and 243 were isolated and tested as HCOOH salts; compounds 246, 247, and 248 were isolated and tested as HCl salts.

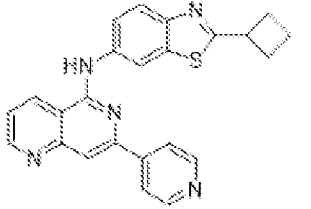
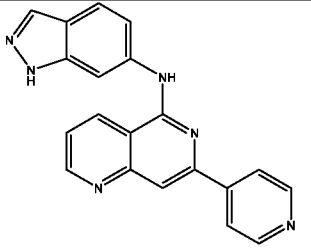
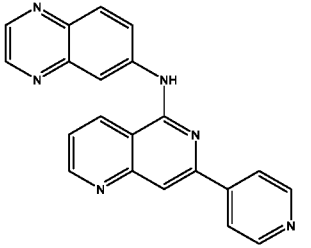
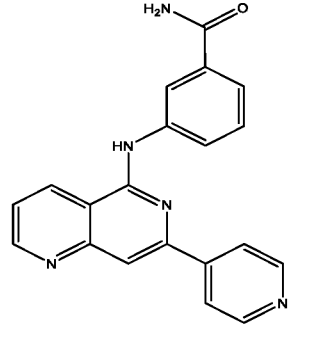
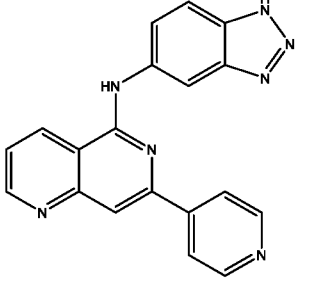
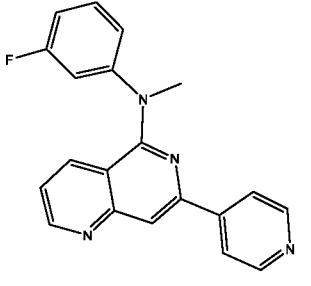
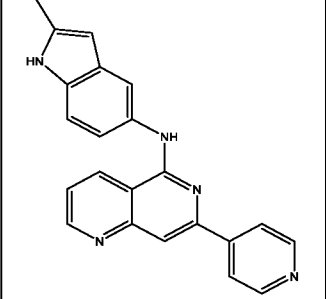
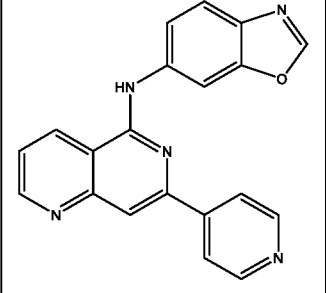
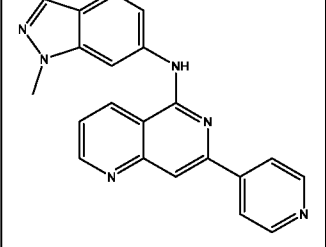
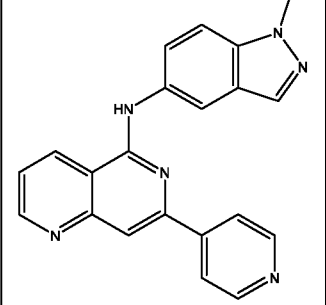
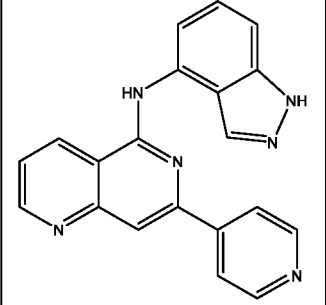
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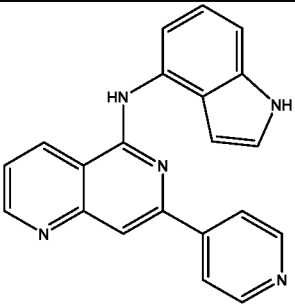
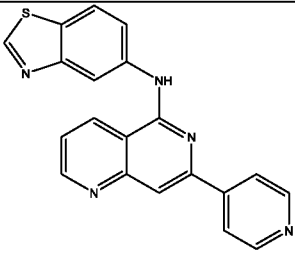
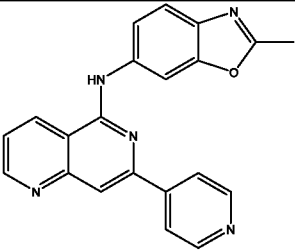
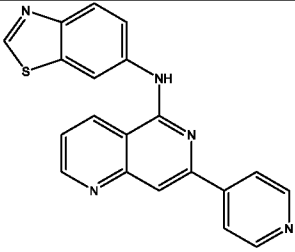
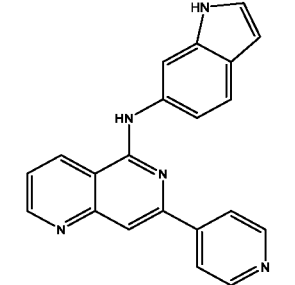
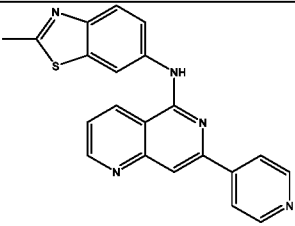
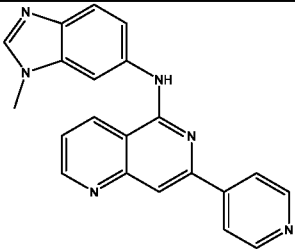
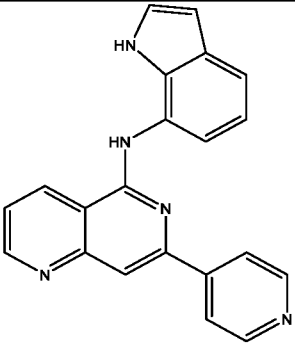
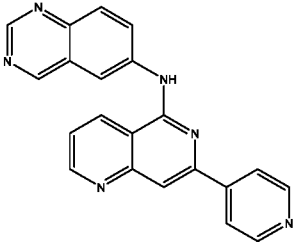
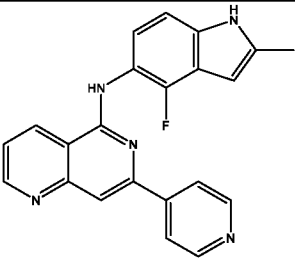
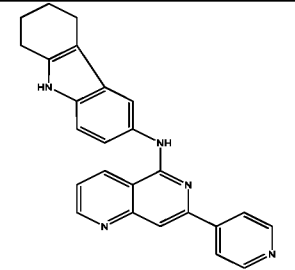
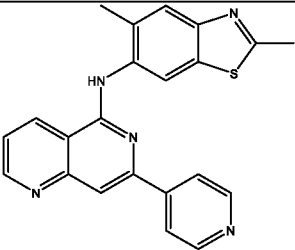
The following compounds shown in Table 5a may prepared using chemical routes that would be readily apparent to one of ordinary skill in the art from readily available starting materials.

Table 5a

10

No.	BC Code	Structure	No.	BC Code	Structure
400	BC18858		401	BC18859	

402	BC18860	
	BC191500	
	BC191501	
	BC191502	
	BC191503	
	BC191504	
	BC191505	
	BC191507	
	BC191508	
	BC191509	
	BC191510	

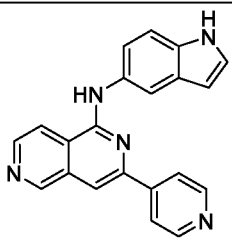
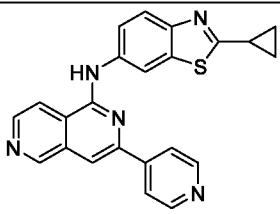
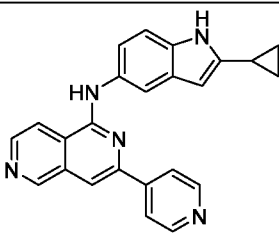
	BC191511	
	BC191512	
	BC191513	
	BC191514	
	BC191515	
	BC191516	
	BC191517	
	BC191518	
	BC191519	
	BC191520	
	BC191521	
	BC191522	

	BC191524	
	BC191525	
	BC191526	
	BC191527	
	BC191528	
	BC191529	
	BC191530	
	BC191531	
	BC191532	
	BC191533	

	BC191534	
	BC191535	
	BC191536	
	BC191537	
	BC191538	
	BC191539	
	BC191540	
	BC191541	
	BC191542	
	BC191543	
	BC191544	

The following compounds shown in Table 6 may prepared using chemical routes that would be readily apparent to one of ordinary skill in the art from readily available starting materials.

Table 6

No .	BC code	Structure	
397	BC18855		
398	BC18856		5
399	BC18857		

Note: Compounds 397, 398, and 399 were isolated and tested as HCl salts.

Example 2 – Assay results

Assay protocol

10 Approximately 2500 primary and immortalized human bronchial epithelial cells (BEAS-2B) stably expressing TFEB-EGFP in 25 μ L of HITEs media with 10% FBS were dispensed into 384 well plate (Black with glass bottom) and incubated for 8 hours. Compound serial dilution (DMEM low glucose media with 2% FBS, 25 μ L volume) were prepared using a robotic liquid handler. Compound solution were then

15 added to the cell plate and incubated for 18 hours. Cells were then fixed with 4% PFA followed by DAPI staining. TFEB localization was imaged on the GFP channel along with the DAPI signal using a Cytation 5 high content imager. Images were processed through Biotek Gen5 software. Specifically, the DAPI signal was used as the primary mask to quantify the nuclear TFEB-GFP signal. Cytosolic TFEB-GFP signal was

20 quantified through expanding the primary mask. The TFEB nuclear/cytosol ratios were calculated from nuclear TFEB-GFP signal/cytosol TFEB-GFP signal, which determined the compound efficacies.

Compounds efficacies (μ M) were determined by the minimal compound concentration needed to increase TFEB nuclear/cytosol ratio by 25%. Activity: “+”

equals $> 25 \mu\text{M}$; “++” equals between $\leq 25 \mu\text{M}$ and $> 1 \mu\text{M}$; and “+++” equals $\leq 1 \mu\text{M}$.

Toxicity was determined by determining the compound concentration needed to induce greater than 50 percent of cell loss. For toxicity, cell loss of greater than 50 percent at a concentration that equals or is greater than $25 \mu\text{M}$ was represented as “+”; cell loss of greater than 50 percent at a concentration less than $25 \mu\text{M}$ and greater than $1 \mu\text{M}$ was represented as “++”; and cell loss of greater than 50 percent at a concentration that equals or is less than $1 \mu\text{M}$ was represented as “+++.” The assay results for compounds 1-202, 214-248, 332, 333, and 352-402 are shown in Table A.

10

Table A. Compound efficacy and toxicity results.

No.	BC code	efficacy	toxicity	No.	BC code	efficacy	toxicity
1	BC18607	+++	+	23	BC18639	+++	+
2	BC18608	+++	+	24	BC18640	+++	+
3	BC18612	+++	+	25	BC18641	+++	++
4	BC18614	+++	+++	26	BC18642	+++	+++
5	BC18615	+	+	27	BC18643	+++	+
6	BC18616	+	+	28	BC18644	+	+
7	BC18617	+	+	29	BC18645	++	+
8	BC18618	+	+	30	BC18646	+++	+++
9	BC18619	+	+	31	BC18647	+++	+++
10	BC18625	+	+	32	BC18648	+++	+++
11	BC18626	+++	+	33	BC18649	+	+
12	BC18627	+++	+	34	BC18652	+++	+
13	BC18628	+	+	35	BC18653	+++	++
14	BC18629	+	+	36	BC18654	+	+
15	BC18630	+++	+	37	BC18655	++	+
16	BC18630 HCl salt	+++	+	38	BC18656	+	+
17	BC18631	+	+	39	BC18657	+	+
18	BC18633	+	+	40	BC18658	++	+
19	BC18634	+	+	41	BC18659	++	++
20	BC18635	++	+	42	BC18660	+++	+
21	BC18636	+	+	43	BC18663	++	+
22	BC18637	+	+	44	BC18664	+++	+
				45	BC18665	+	+

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No.	BC code	efficacy	toxicity
46	BC18666	+	+
47	BC18667	+++	+++
48	BC18668	+	+
49	BC18669	+	+
50	BC18670	+	+
51	BC18671	+	+
52	BC18672	+	+
53	BC18673	+	+
54	BC18674	+	+
55	BC18675	+	+
56	BC18676	++	+
57	BC18677	+++	+
58	BC18678	++	+
59	BC18679	++	+
60	BC18680	+	+
61	BC18681	+++	++
62	BC18682	+++	+++
63	BC18683	+	+
64	BC18684	++	++
65	BC18685	+	+
66	BC18686	+	+
67	BC18687	+	+
68	BC18688	+	+
69	BC18689	+	+
70	BC18690	+++	+
71	BC18693	+++	+
72	BC18695	+++	+++
73	BC18697	+++	+++
74	BC18698	+++	++
75	BC18702	+	+
76	BC18703	+	+
77	BC18704	+++	+
78	BC18705	++	+
79	BC18706	+	+
80	BC18707	++	+

No.	BC code	efficacy	toxicity
81	BC18708	+++	++
82	BC18709	+++	+
83	BC18711	++	+
84	BC18713	+++	+
85	BC18714	+++	+
86	BC18717	+++	+++
87	BC18718	+	+
88	BC18720	+	+
89	BC18722	++	++
90	BC18724	+++	+
91	BC18725	+++	+
92	BC18726	++	+
93	BC18727	+	+
94	BC18728	+++	+
95	BC18729	+	+
96	BC18730	+	+
97	BC18731	+++	+
98	BC18732	+++	+
99	BC18733	+++	+
100	BC18734	+	+
101	BC18735	+	+
102	BC18736	+++	+
103	BC18737	+++	+
104	BC18738	+++	+
105	BC18739	+	+
106	BC18740	+	+
107	BC18742	+	+
108	BC18743	+++	+
109	BC18744	+++	+
110	BC18745	+++	+
111	BC18746	+	+
112	BC18747	+++	+
113	BC18748	+++	++
114	BC18749	+++	++
115	BC18750	+	+

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No.	BC code	efficacy	toxicity
116	BC18752	+++	+
117	BC18754	+++	+
118	BC18755	++	+
119	BC18756	+	+
120	BC18757	+	+
121	BC18758	+	+
122	BC18759	+	+
123	BC18760	++	+
124	BC18761	+++	+
125	BC18762	++	+
126	BC18763	++	+
127	BC18764	++	+
128	BC18765	+++	+
129	BC18766	+++	+
130	BC18767	+++	+
131	BC18768	+++	+
132	BC18769	+++	+
133	BC18770	+++	+
134	BC18771	+++	+
135	BC18772	++	+
136	BC18773	+++	+
137	BC18774	+++	+
138	BC18775	+++	+
139	BC18776	+	+
140	BC18778	+	+
141	BC18779	+++	++
142	BC18780	+++	+
143	BC18782	+++	+
144	BC18783	+	+
145	BC18784	+++	+
146	BC18785	+++	+
147	BC18786	++	+
148	BC18787	+++	+

No.	BC code	efficacy	toxicity
149	BC18788	++	++
150	BC18789	+++	++
151	BC18790	+++	+
152	BC18791	++	+
153	BC18792	++	+
154	BC18793	+++	+
155	BC18794	+++	+
156	BC18795	+++	+
157	BC18796	+++	++
158	BC18797	+++	+
159	BC1820	+	+
160	BC18200	+++	++
161	BC18201	+	+
162	BC18202	+	+
163	BC18203	+	+
164	BC18204	+	+
165	BC18205	+	+
166	BC18206	+	+
167	BC18207	++	+
168	BC18208	+	+
169	BC18209	+	+
170	BC18210	+	+
171	BC18211	+	+
172	BC18212	+	+
173	BC18213	+	+
174	BC18214	+	+
175	BC18215	+	+
176	BC18216	++	+
177	BC18217	+	+
178	BC1834	+++	+
179	BC18601	++	+
180	BC18602	+	+
181	BC18603	+++	+

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No.	BC code	efficacy	toxicity
182	BC18604	+	+
183	BC18605	++	+
184	BC18606	++	+
185	BC18609	+++	+
186	BC18610	+++	+
187	BC18611	+++	+
188	BC18613	+	+
189	BC18623	++	+
190	BC18624	++	+
191	BC18632	+++	+
192	BC18651	+++	+
193	BC18661	++	++
194	BC18715	+++	+
195	BC1816	+	+
196	BC1835	+	+
197	BC1836	+	+
198	BC1837	+	+
199	BC1838	+	+
200	BC1839	++	+
201	BC1840	+	+
202	BC1841	+	+
214	BC1770	+	+
215	BC1771	++	++
216	BC1772	+	+
217	BC1773	+	+
218	BC1774	+	+
219	BC1775	+	+
220	BC1776	+	+
221	BC1777	+	+
222	BC1753	++	++
223	BC1780	+	+
224	BC1781	+	+
225	BC1782	+	+

No.	BC code	efficacy	toxicity
226	BC1783	+	+
227	BC1784	+	+
228	BC1785	+	+
229	BC1786	+	+
230	BC1787	+	+
231	BC1811	++	+
232	BC1812	+	+
233	BC1813	+	+
234	BC1814	++	+
235	BC1815	++	+
236	BC1817	++	+
237	BC1818	++	+
238	BC1819	+	+
239	BC18842	++	+
240	BC18846	+++	+
241	BC18847	+++	+
242	BC18848	+++	+
243	BC18849	+++	+
244	BC18850	+++	+
245	BC18851	+++	+
246	BC18852	+++	+
247	BC18853	++	+
248	BC18854	++	+
332	BC191183/ BC18861	+++	+
333	BC191184/ BC18862	+++	+
352	BC18795	++	+
353	BC18796	++	+
354	BC18797	+	+
355	BC18798	++	+
356	BC18799	+++	+
357	BC18800	+	+
358	BC18801	++	+
359	BC18802	+	+
360	BC18803	+	+

No.	BC code	efficacy	toxicity
361	BC18804	++	+
362	BC18805	+	+
363	BC18806	+++	+
364	BC18807	+	+
365	BC18808	+++	+
366	BC18809	+	+
367	BC18810	++	+
368	BC18811	++	+
369	BC18812	+	+
370	BC18814	+++	+
371	BC18817	+++	+
372	BC18818	+++	+
373	BC18819	++	+
374	BC18820	++	+
375	BC18821	+++	+
376	BC18822	+++	+
377	BC18823	++	+
378	BC18824	+++	+
379	BC18825	+++	+
380	BC18826	++	+
381	BC18827	+++	+

No.	BC code	efficacy	toxicity
382	BC18828	+	+
383	BC18829	++	+
384	BC18830	+++	+
385	BC18831	++	+
386	BC18832	+++	+
387	BC18833	+	+
388	BC18834	+	+
389	BC18835	+	+
390	BC18836	+	+
391	BC18837	+++	+
392	BC18838	+	+
393	BC18839	++	+
394	BC18840	+	+
395	BC18841	+++	+
396	BC18845	+++	+
397	BC18855	++	+
398	BC18856	+++	+
399	BC18857	+++	+
400	BC18858	+++	+
401	BC18859	+++	+
402	BC18860	+++	+

Example 3 – Using BC1753 to increase TFEB polypeptide levels

BC1753 (Figure 2A) was tested for its ability to increase TFEB polypeptide levels. Briefly, murine lung epithelial cells (MLE12) stably expressing TFEB-EGFP were treated with BC1753 in a dose dependent manner for 18 hours. Cells were then collected and assayed by immunoblotting for TFEB-GFP protein levels (Figure 2B). Murine lung epithelial cells (MLE12) stably expressing TFEB-EGFP were treated with BC1753 in a dose dependent manner for 18 hours. Cells were then fixed with 4% PFA followed by DAPI staining. TFEB localization was imaged on the GFP channel along with the DAPI signal using a Nikon A1 confocal microscope (Figure 2C). BC1753 drastically increased total TFEB polypeptide levels within cells (Figure 2B) and increased nuclear TFEB polypeptide accumulation (Figure 2C).

Example 4 – Compounds for increasing TFEB polypeptide levels
within the nucleus of cells

A high-content imaging screen was conducted using Beas2B cells that stably express GFP-TFEB. This approach demonstrated robust and accurate measurement of TFEB nuclear/cytosol ratio upon various compound treatments (Figure 3).

Example 5 – Increasing lysosome quantity, lysosomal protein expression,
and secretion of lysosomal enzymes

Compounds 178 (BC1834) and/or 160 (BC18200) at the indicated concentrations were found to increase lysosome quantity (Figures 4A-B), to increase lysosomal protein expression (Figure 5A), and to increase secretion of the lysosomal enzyme beta hexosaminidase (Figure 5B).

Example 6 – Using compounds provided herein to reduce the level of Huntingtin
polypeptides

Compound 178 (BC1834) was tested for the ability to reduce Huntingtin polypeptide levels within cells. Briefly, Compound 178 was administered to SH5Y cells stably expressing GFP-Huntingtin (72Q). As shown in Figures 6A-B, Compound 178 dose dependently reduced GFP-Huntingtin polypeptide levels. These results demonstrate that the compounds provided herein can be used to treat neurological conditions such as Huntington's disease.

Example 7 – *In vivo* effects

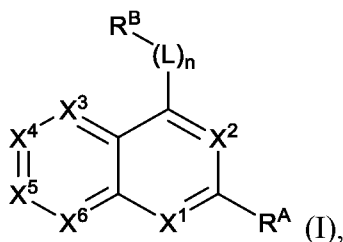
Female C57BL6 mice were i.p. injected with Compound 15 (50 mg/kg/day) for 4 days. Mice were then i.v. injected with dextran blue. 24 hours later, mice were sacrificed, and liver samples were removed and imaged through confocal microscopy. As shown in Figure 7, Compound 15 treatment drastically increased lysosomal dextran blue signal and lamp2 staining (pseudo-colored white). These results demonstrate that the compounds provided herein can increase *in vivo* lysosomal number and activity.

OTHER EMBODIMENTS

It is to be understood that while the present application has been described in conjunction with the detailed description thereof, the foregoing description is intended
5 to illustrate and not limit the scope of the present application, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for increasing TFEB polypeptide levels within a nucleus of a cell within a mammal, wherein said method comprises administering, to said mammal, a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from O, S, S(=O)₂, C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

each R^N is independently selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

n is an integer selected from 1, 2, and 3;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

X³ is selected from N, N⁺-O⁻, and CR³;

X⁴ is selected from N, N⁺-O⁻, and CR⁴;

X⁵ is selected from N, N⁺-O⁻, and CR⁵;

X⁶ is selected from N, N⁺-O⁻, and CR⁶;

provided that no more than four of X¹, X², X³, X⁴, X⁵, and X⁶ are N;

each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from

CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and N(R^N)-Cy^{A1};

Cy^{A1} is selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and Cy¹, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to L which is N(R^N), R^B and R^N together with the N atom to which they are attached form 4-14 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₄ cycloalkyl, 5-10 membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2};

R^{Cy1} and R^{Cy2} are each independently selected from oxo, halo, CN, NO₂, Cy², C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy², halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each Cy² is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is

optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}S(O)₂R^{b2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

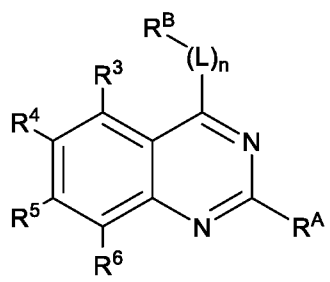
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino,

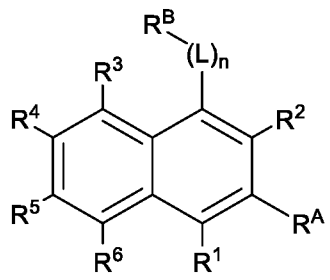
di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

2. The method of claim 1, wherein R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{al}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{al}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{al}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{al}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; and each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2}.
3. The method of claim 1 or 2, wherein n is 1.
4. The method of any one of claims 1-3, wherein L is C₁₋₃ alkylene, which is optionally substituted with OH.
5. The method of any one of claims 1-3, wherein L is C(=O).
6. The method of any one of claims 1-3, wherein L is N(R^N).
7. The method of claim 6, wherein R^N is selected from H and C₁₋₆ alkyl.
8. The method of claim 6, wherein L is NH.
9. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



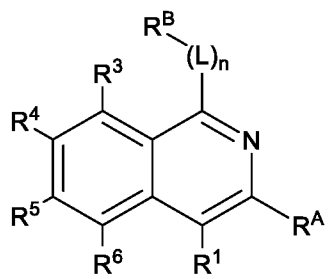
or a pharmaceutically acceptable salt thereof.

10. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



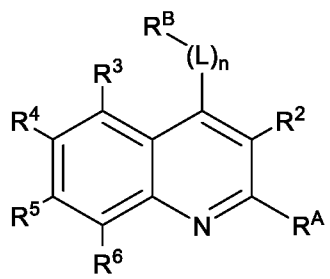
or a pharmaceutically acceptable salt thereof.

11. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



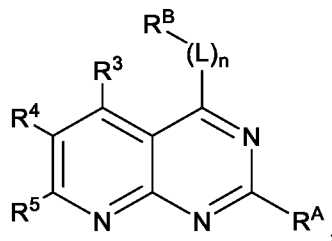
or a pharmaceutically acceptable salt thereof.

12. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



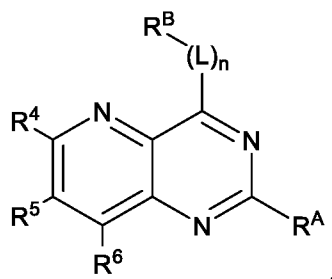
or a pharmaceutically acceptable salt thereof.

13. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



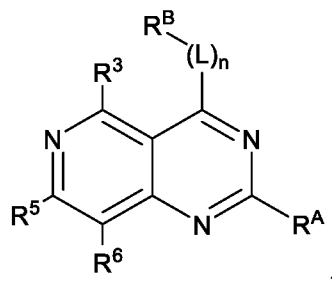
or a pharmaceutically acceptable salt thereof.

14. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



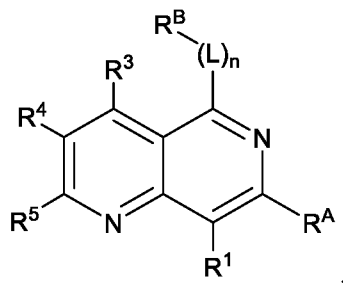
or a pharmaceutically acceptable salt thereof.

15. The method of any one of claims 1-8, wherein the compound of Formula (I) has formula:



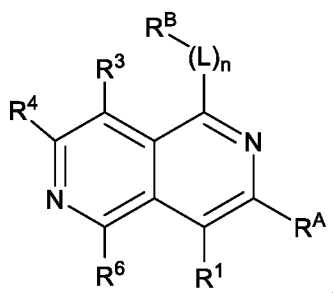
or a pharmaceutically acceptable salt thereof.

16. The method of any one of claim 1-8, wherein the compound of Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

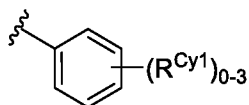
17. The method of any one of claim 1-8, wherein the compound of Formula (I) has formula:



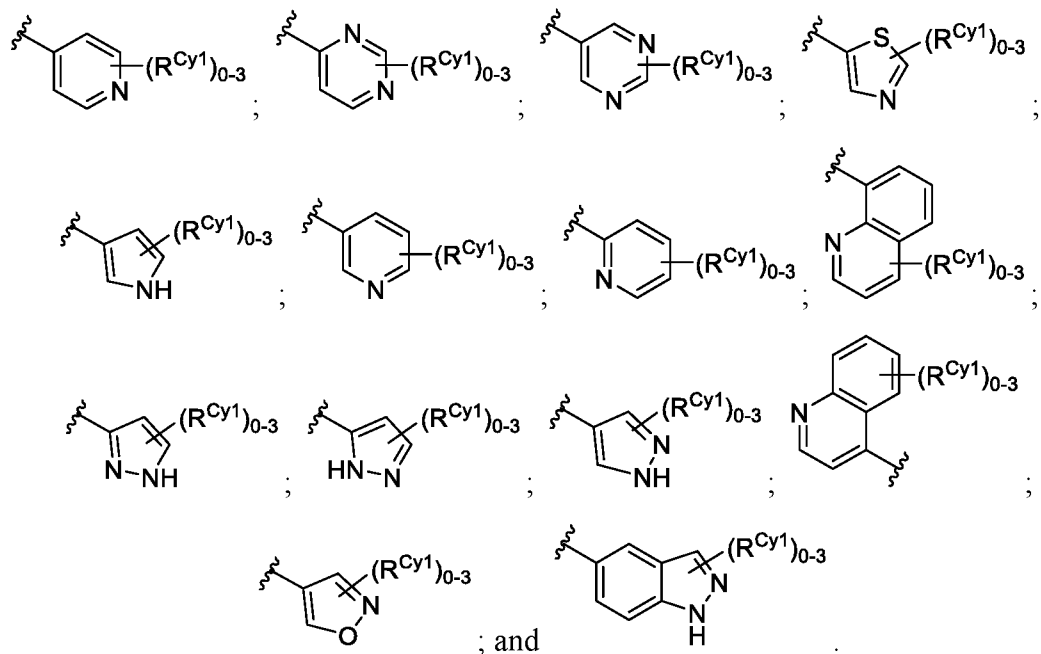
or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-17, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 , if present in the compound of Formula (I), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.
19. The method of any one of claims 1-17, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 , if present in the compound of Formula (I), is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.
20. The method of any one of claims 1-17, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 , if present in the compound of Formula (I), is independently selected from H, halo, CN, C_{1-6} alkyl, OR^{a1} , $NR^{c1}R^{d1}$, and $S(O)_2R^{b1}$.

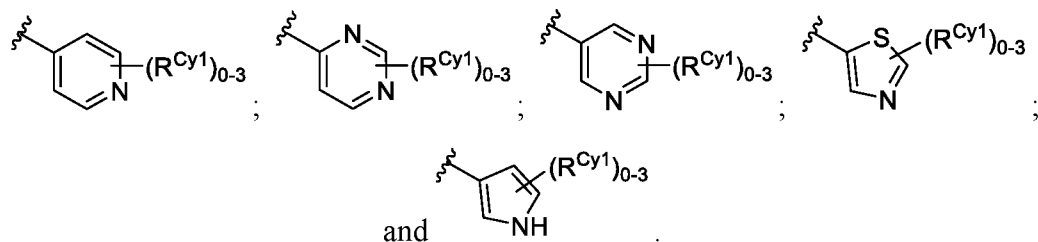
21. The method of claim 20, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.
22. The method of any one of claims 1-21, wherein R^A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} .
23. The method of any one of claims 1-21, wherein R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
24. The method of claim 23, wherein R^A is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
25. The method of claim 23, wherein R^A is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
26. The method of claim 23, wherein R^A is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
27. The method of any one of claims 1-21, wherein R^A is $O-Cy^{A1}$.
28. The method of any one of claims 1-21, wherein R^A is $NH-Cy^{A1}$.
29. The method of claim 27 or 28, wherein Cy^{A1} is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
30. The method of any one of claims 22-29, wherein the C_{6-10} aryl has the formula:



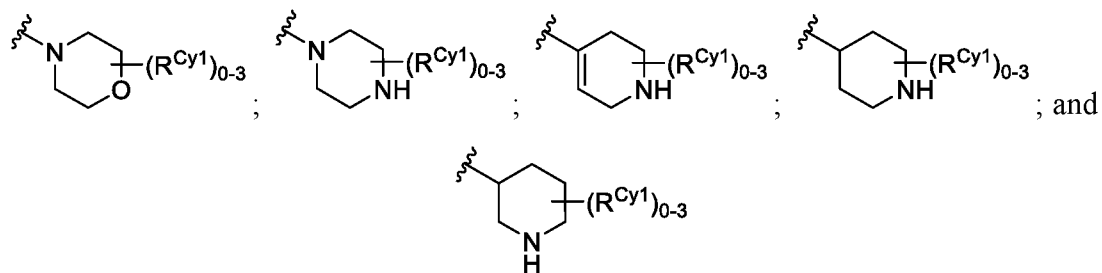
31. The method of any one of claims 22-29, wherein the 5-10 membered heteroaryl has the formula selected from:



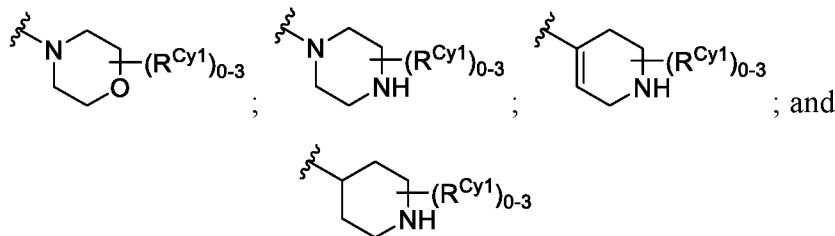
32. The method of any one of claims 22-29, wherein the 5-10 membered heteroaryl has the formula selected from:



33. The method of any one of claims 22-29, wherein the 4-10 membered heterocycloalkyl has the formula selected from:



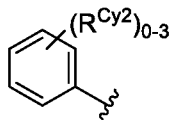
34. The method of any one of claims 22-29, wherein the 4-10 membered heterocycloalkyl has the formula selected from:



35. The method of any one of claims 1-34, wherein each R^{Cy1} is independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.
36. The method of any one of claims 1-34, wherein each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} .
37. The method of any one of claims 1-34, wherein each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$.
38. The method of any one of claims 1-37, wherein R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.
39. The method of any one of claims 1-38, wherein R^B is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.
40. The method of any one of claims 1-38, wherein R^B is Cy^1 .

41. The method of any one of claims 1-40, wherein Cy^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

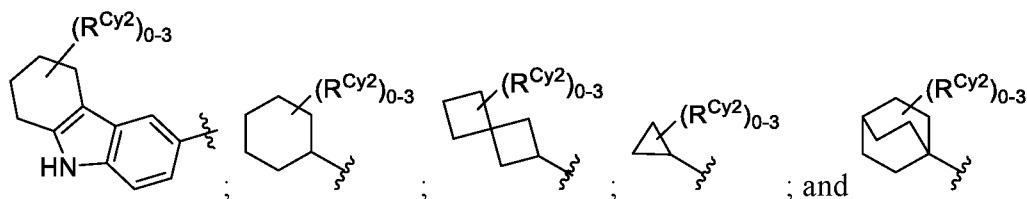
42. The method of claim 41, wherein the C_{6-10} aryl has formula:



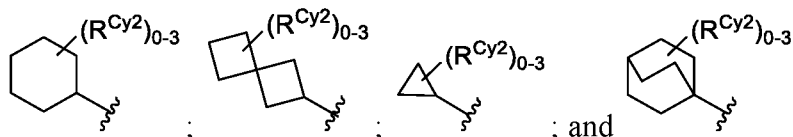
43. The method of any one of claims 1-40, wherein Cy^1 is C_{3-14} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

44. The method of any one of claims 1-40, wherein Cy^1 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

45. The method of claim 43, wherein the C_{3-14} cycloalkyl has the formula selected from:



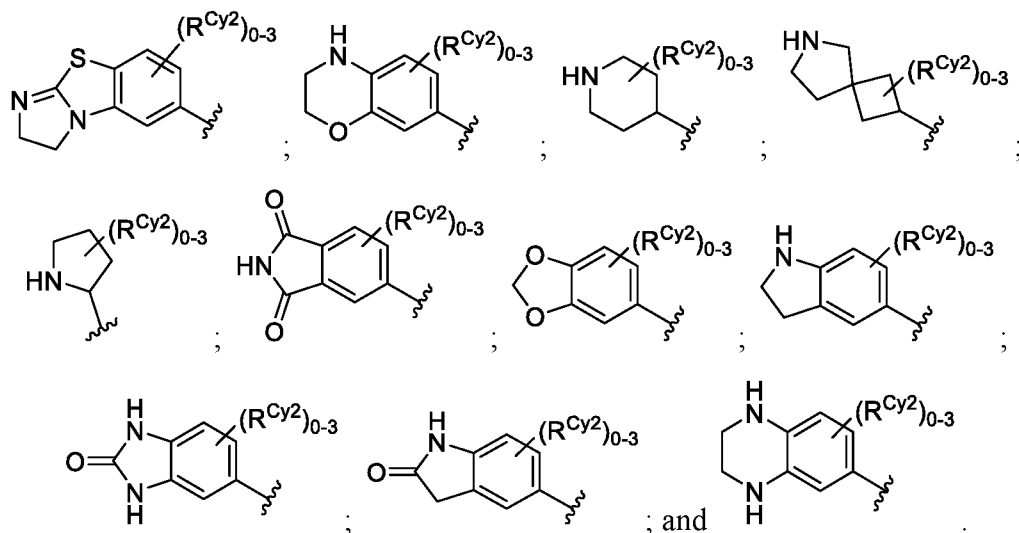
46. The method of claim 44, wherein the C_{3-10} cycloalkyl has the formula selected from:



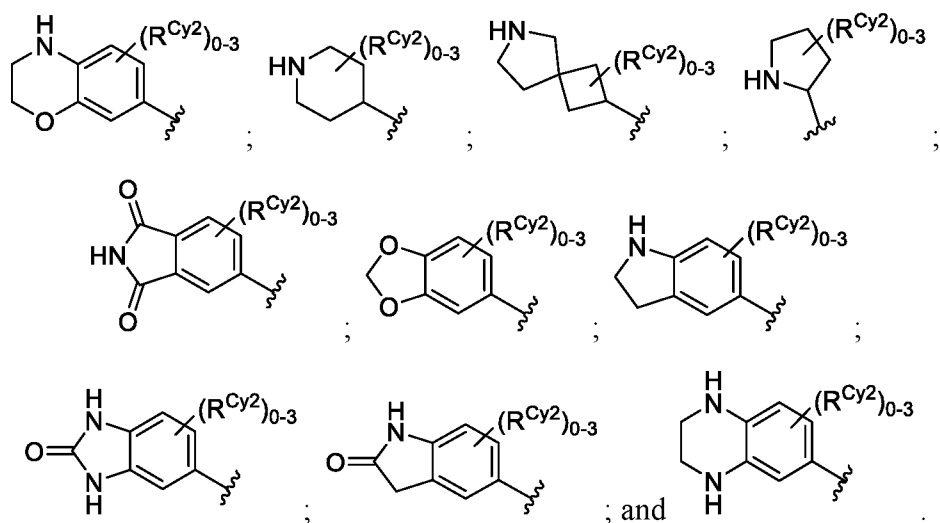
47. The method of any one of claims 1-40, wherein Cy^1 is 4-14 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

48. The method of any one of claims 1-40, wherein Cy^1 is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

49. The method of claim 47, wherein the 4-14 membered heterocycloalkyl has the formula selected from:

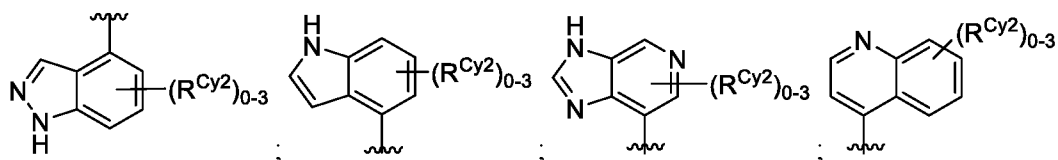


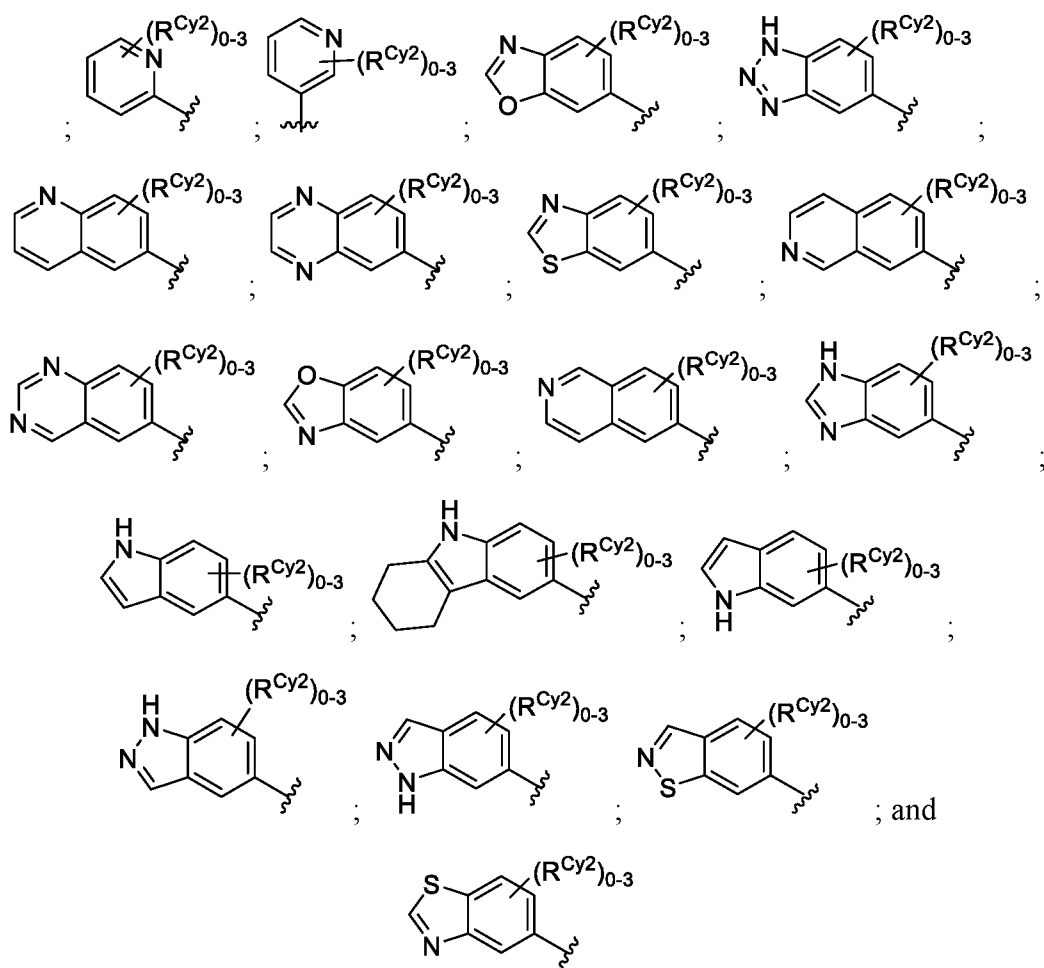
50. The method of claim 48, wherein the 4-10 membered heterocycloalkyl has the formula selected from:



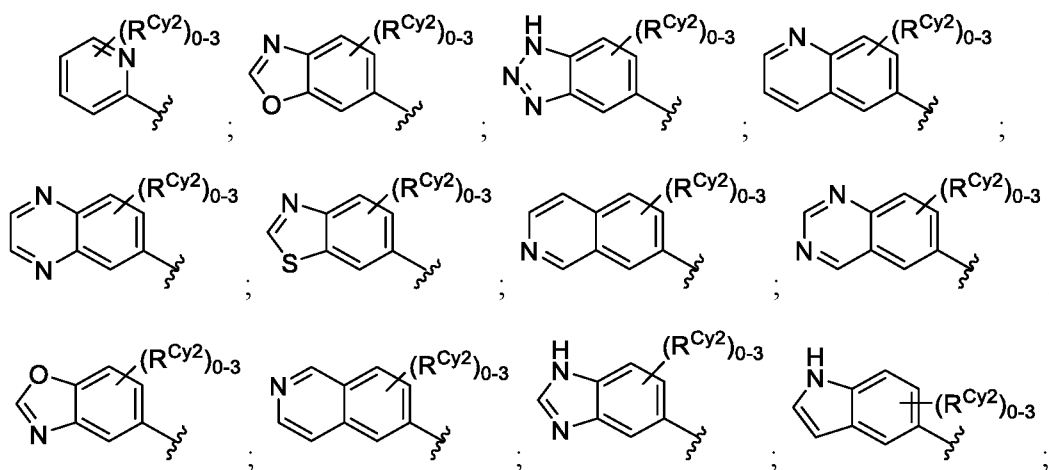
51. The method of any one of claims 1-40, wherein Cy^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

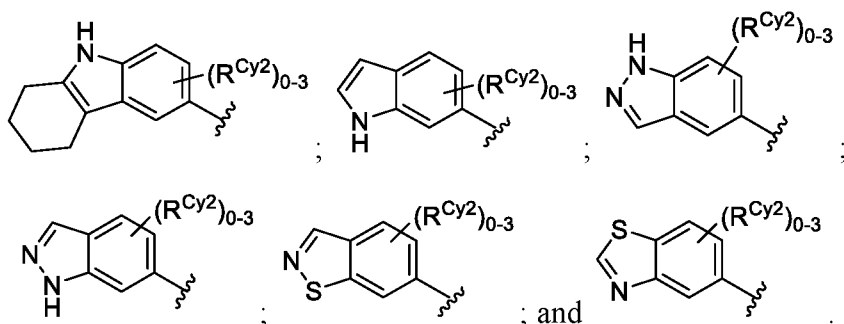
52. The method of claim 51, wherein the 5-10 membered heteroaryl has the formula selected from:





53. The method of claim 51, wherein the 5-10 membered heteroaryl has the formula selected from:





54. The method of any one of claims 1-53, wherein each R^{Cy2} is independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.
55. The method of any one of claims 1-53, wherein each R^{Cy2} is independently selected from halo, Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, and $S(O)_2R^{b2}$.
56. The method of any one of claims 1-53, wherein each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$.
57. The method of any one of claims 1-56, wherein each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.
58. The method of any one of claims 1-57, wherein R^B is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} ; and R^A is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
59. The method of any one of claims 1-57, wherein R^B is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} ; and R^A is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .

60. The method of any one of claims 1-57, wherein R^B is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} ; and R^A is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
61. The method of any one of claims 1-57, wherein R^B is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} ; and R^A is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .
62. The method of claim 1, wherein:
- n is 1;
 - L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;
 - R^N is selected from H and C_{1-6} alkyl;
 - R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, C_{1-6} alkyl, OR^{a1} , $NR^{c1}R^{d1}$, and $S(O)_2R^{b1}$;
 - R^A is selected from Cy^{A1} , $O-Cy^{A1}$, and $NH-Cy^{A1}$;
 - each Cy^{A1} is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;
 - R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;
 - or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-14 membered heterocycloalkyl, which is optionally substituted with Cy^1 , C_{1-6} alkyl, OR^{a1} , and halo;
 - each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} ;
 - each Cy^1 is independently selected from C_{6-10} aryl, C_{3-14} cycloalkyl, 5-10 membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} ;

each R^{Cy2} is independently selected from halo, Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, and $S(O)_2R^{b2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

63. The method of claim 1, wherein:

n is 1;

L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^N is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, C_{1-6} alkyl, OR^{a1} , $NR^{c1}R^{d1}$, and $S(O)_2R^{b1}$;

R^A is selected from Cy^{A1} , $O-Cy^{A1}$, and $NH-Cy^{A1}$;

each Cy^{A1} is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} ;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

64. The method of claim 1, wherein:

n is 1;

L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^N is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and OR^{a1} ;

R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$;

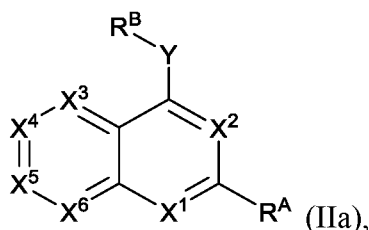
each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

65. The method of claim 1, wherein the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 1a, Table 2, Table 3, Table 5, Table 5a, and Table 6, or a pharmaceutically acceptable salt thereof.
66. The method of claim 1, wherein the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 1a, Table 2, Table 3, Table 5, and Table 6, or a pharmaceutically acceptable salt thereof.
67. The method of claim 1, wherein the compound of Formula (I) is selected from any one of the compounds in Table 1, Table 2, and Table 3, or a pharmaceutically acceptable salt thereof.
68. The method of any one of claims 1-67, wherein said mammal is a human.
69. A pharmaceutical composition comprising a compound of Formula (I), as recited in any one of claims 1-67, or a pharmaceutically acceptable salt thereof.

70. The pharmaceutical composition of claim 69, wherein said pharmaceutical composition further comprises an approved enzyme replacement therapy for LSDs, an approved therapy for a neurodegenerative disease, or another anti-aging medicine.

71. A compound of Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from C(=O) and C(R⁷)(R⁸);

R⁷ and R⁸ are each independently selected from H, halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

X³ is selected from N, N⁺-O⁻, and CR³;

X⁴ is selected from N, N⁺-O⁻, and CR⁴;

X⁵ is selected from N, N⁺-O⁻, and CR⁵;

X⁶ is selected from N, N⁺-O⁻, and CR⁶;

provided that no more than four of X¹, X², X³, X⁴, X⁵, and X⁶ are N;

R¹, R², R³, R⁴, R⁵, and R⁶ are each independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{bl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO₂, OR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{bl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl};

R^A is selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cyl};

R^B is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and Cy^l, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted

with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$,

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} ,

each R^{Cy1} and R^{Cy2} is independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$,

each Cy^2 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$,

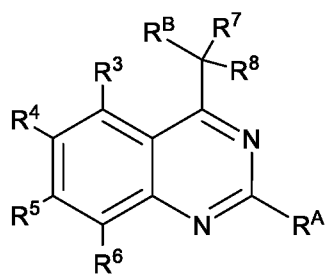
each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkylene, C_{3-10} cycloalkyl- C_{1-4} alkylene, (5-10 membered heteroaryl)- C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)- C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkylene, C_{3-10} cycloalkyl- C_{1-4} alkylene, (5-10 membered heteroaryl)- C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g ;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfanyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

72. The compound of claim 71, wherein the compound of Formula (IIa) has formula:

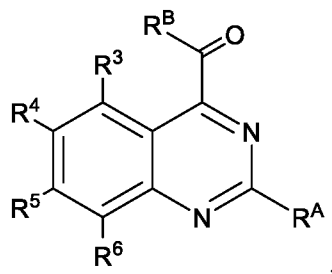


or a pharmaceutically acceptable salt thereof.

73. The compound of claim 71 or 72, wherein R⁷ is H, and R⁸ is selected from H, halo, CN, NO₂, OH, and C₁₋₃ alkoxy.

74. The compound of claim 73, wherein R⁸ is selected from H and OH.

75. The compound of claim 71, wherein:



or a pharmaceutically acceptable salt thereof.

76. The compound of any one of claims 71-75, wherein R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

77. The compound of claim 76, wherein R^3 , R^4 , R^5 , and R^6 are each H.

78. The compound of any one of claims 71-77, wherein R^B is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .

79. The compound of claim 78, wherein R^B is C_{6-10} aryl, optionally substituted with halo.

80. The compound of any one of claims 71-79, wherein R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} .

81. The compound of claim 80, wherein R^A is 5-10 membered heteroaryl, optionally substituted with halo, NO_2 , C_{1-6} alkyl, or C_{1-6} alkoxy.

82. The compound of claim 71, wherein:

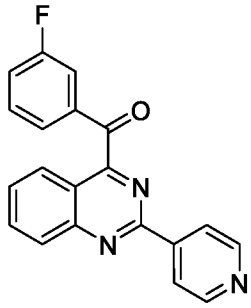
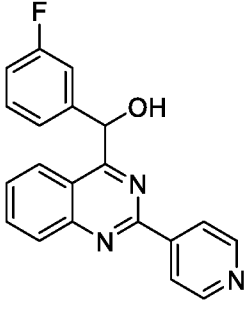
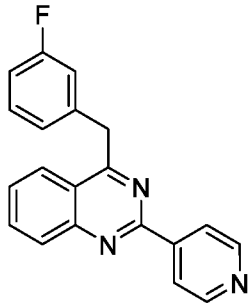
R^7 is H; and R^8 is selected from H and OH;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^B is C_{6-10} aryl, optionally substituted with halo; and

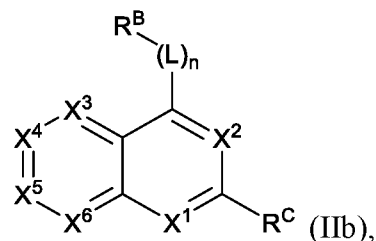
R^A is 5-10 membered heteroaryl, optionally substituted with halo, NO_2 , C_{1-6} alkyl, or C_{1-6} alkoxy.

83. The compound of claim 71, wherein the compound is selected from:

BC18615	
BC18616	
BC18617	

or a pharmaceutically acceptable salt thereof.

84. A compound of Formula (IIb):



or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from O, S, S(=O)₂, C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

each R^N is independently selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

n is an integer selected from 1, 2, and 3;

X¹ is selected from N, N⁺-O⁻, and CR¹;

X² is selected from N, N⁺-O⁻, and CR²;

X³ is selected from N, N⁺-O⁻, and CR³;

X^4 is selected from N, N^+-O^- , and CR^4 ;

X^5 is selected from N, N^+-O^- , and CR^5 ;

X^6 is selected from N, N^+-O^- , and CR^6 ;

provided that no more than four of X^1 , X^2 , X^3 , X^4 , X^5 , and X^6 are N;

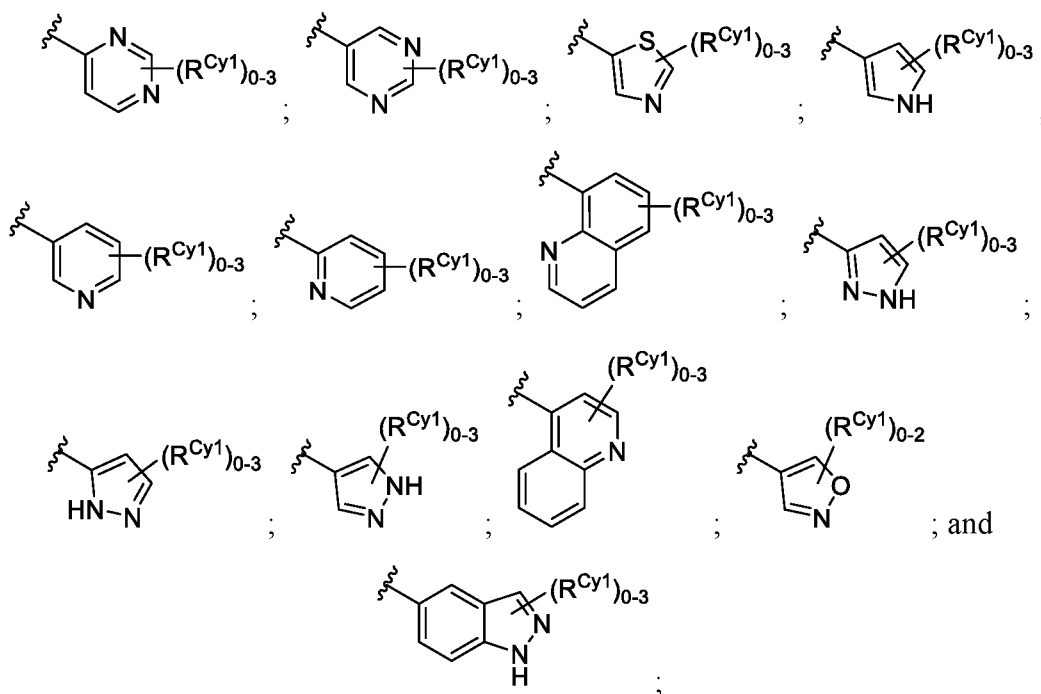
each of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is independently selected from H, halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^C is selected from:

(iii) 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ; and

(iv) a group selected from $O-Cy^{A1}$, $N(R^N)-Cy^{A1}$; and Cy^{A1} ;

each Cy^{A1} is a 5-10 membered heteroaryl group of the formula selected from:



R^B is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted

with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{al} , C(O)R^{b1} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{b1}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{b1}}$, $\text{S(O)}_2\text{R}^{\text{b1}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$,

or, when R^{B} is attached to $\text{N(R}^{\text{N}})$, R^{B} and R^{N} together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{al} , C(O)R^{b1} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{b1}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{b1}}$, $\text{S(O)}_2\text{R}^{\text{b1}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{al} , C(O)R^{b1} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{b1}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{b1}}$, $\text{S(O)}_2\text{R}^{\text{b1}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{d1}}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} ;

R^{Cy1} and R^{Cy2} are each independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , C(O)R^{b2} , $\text{C(O)NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C(O)R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{S(O)}_2\text{R}^{\text{b2}}$, $\text{S(O)}_2\text{R}^{\text{b2}}$, and $\text{S(O)}_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , C(O)R^{b2} , $\text{C(O)NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C(O)R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{S(O)}_2\text{R}^{\text{b2}}$, $\text{S(O)}_2\text{R}^{\text{b2}}$, and $\text{S(O)}_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$;

each Cy^2 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , C(O)R^{b2} , $\text{C(O)NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C(O)R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{S(O)}_2\text{R}^{\text{b2}}$, $\text{S(O)}_2\text{R}^{\text{b2}}$, and $\text{S(O)}_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2 , OR^{a2} , C(O)R^{b2} , $\text{C(O)NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C(O)R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C(O)OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{S(O)}_2\text{R}^{\text{b2}}$, $\text{S(O)}_2\text{R}^{\text{b2}}$, and $\text{S(O)}_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$;

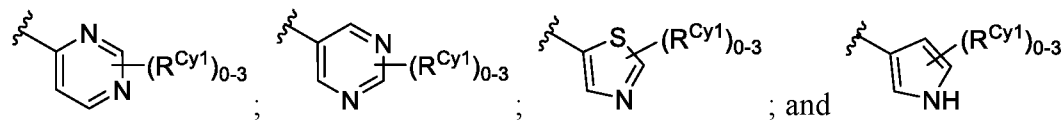
each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g ;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g ;

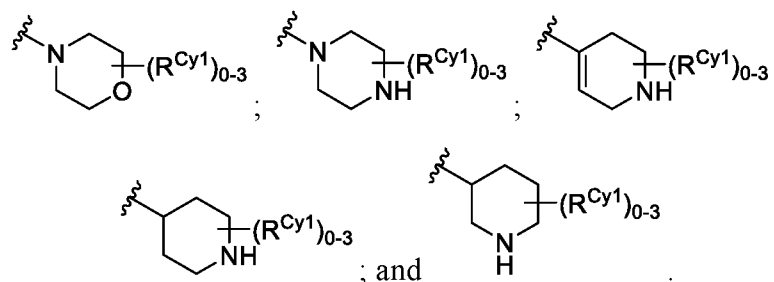
or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g ; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

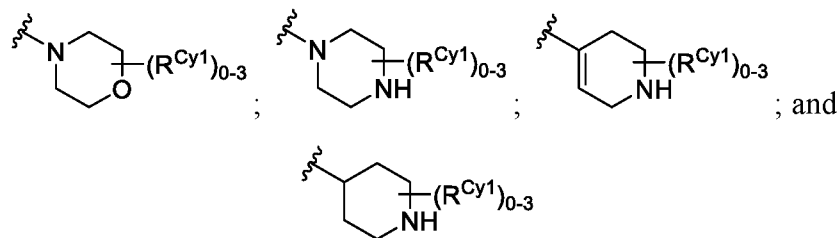
85. The compound of claim 84, wherein R^C is selected from 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ; and a 5-10 membered heteroaryl group of the formula selected from:



86. The compound of claim 84 or 85, wherein the 4-10 membered heterocycloalkyl of R^C has the formula selected from:



87. The compound of any one of claims 84-86, wherein the 4-10 membered heterocycloalkyl of R^C has the formula selected from:



88. The compound of claim 84, wherein:

n is 1;

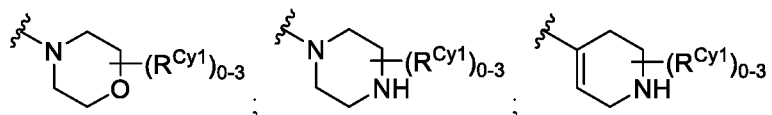
L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH ;

R^N is selected from H and C_{1-6} alkyl;

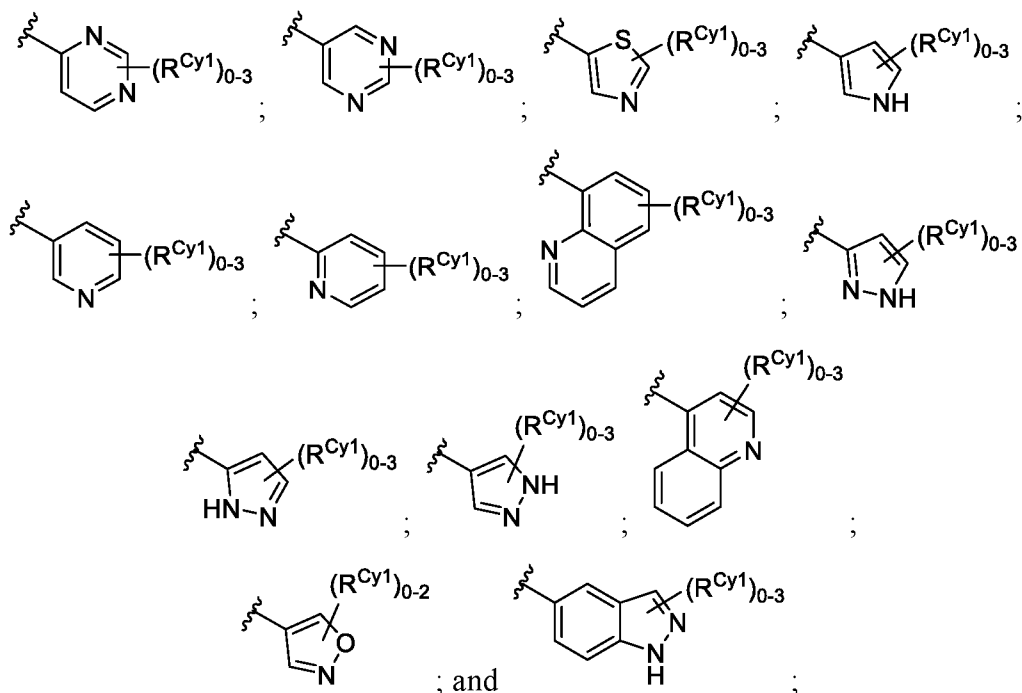
R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H , halo, CN , C_{1-6} alkyl, OR^{a1} , $NR^{c1}R^{d1}$, and $S(O)_2R^{b1}$;

R^C is selected from:

(iii) 4-10 membered heterocycloalkyl selected from:



(iv) a group selected from O-Cy^{A1}, N(R^N)-Cy^{A1}; and Cy^{A1}, wherein each Cy^{A1} is a 5-10 membered heteroaryl group of the formula selected from:



R^B is selected from C₁₋₆ alkyl and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, OR^{a1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to N(R^N), R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1};

each R^{Cy1} is independently selected from halo, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, and S(O)₂R^{b2}, wherein said C₁₋₆ alkyl is optionally substituted with OR^{a2};

each R^{Cy2} is independently selected from halo, CN, C₃₋₁₀ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and NR^{c2}R^d, and

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H and C₁₋₆ alkyl.

89. The compound of claim 84, wherein:

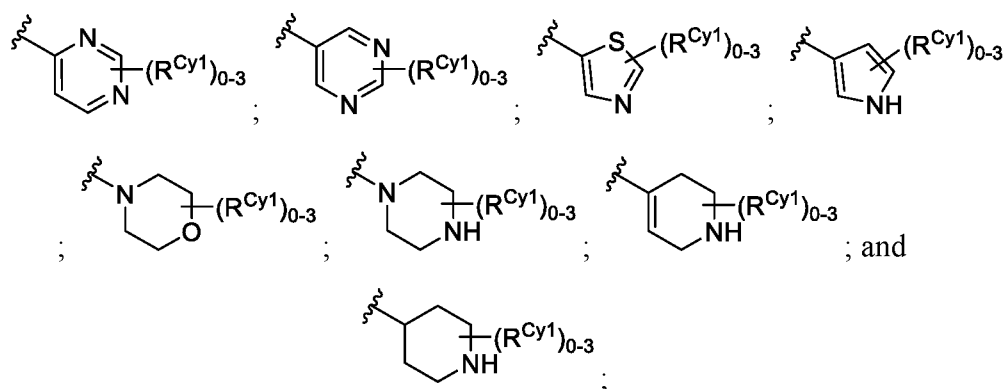
n is 1;

L is selected from C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with OH;

R^N is selected from H and C₁₋₆ alkyl;

R¹, R², R³, R⁴, R⁵, and R⁶ are each independently selected from H, halo, C₁₋₆ alkyl, and OR^{a1};

R^C is selected from:



R^B is selected from C₁₋₆ alkyl and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, OR^{a1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to N(R^N), R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1};

each R^{Cy1} is independently selected from halo, NO₂, C₁₋₆ alkyl, OR^{a2}, and C(O)OR^{a2};

each R^{Cy2} is independently selected from halo, CN, C₃₋₁₀ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and NR^{c2}R^d; and

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H and C₁₋₆ alkyl.

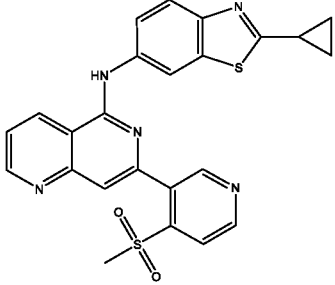
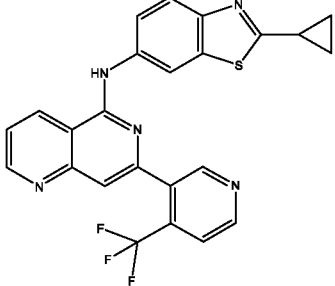
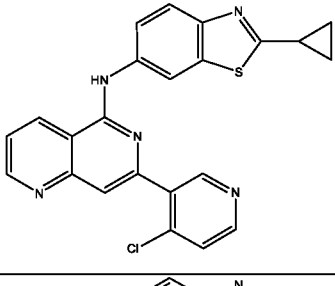
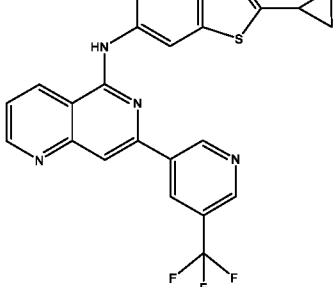
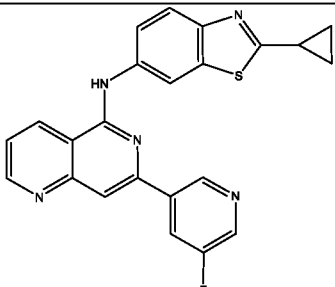
90. The compound of claim 84, wherein the compound of Formula (IIb) is selected from:

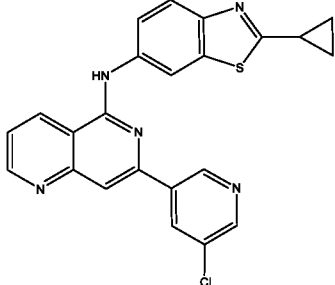
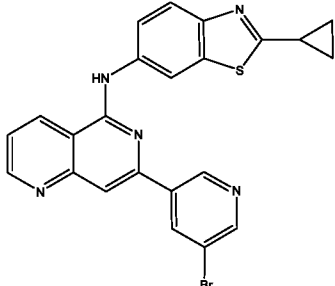
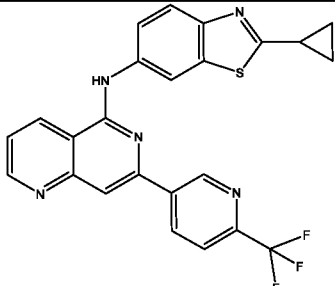
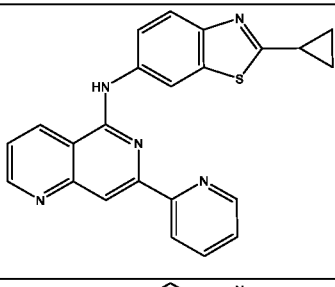
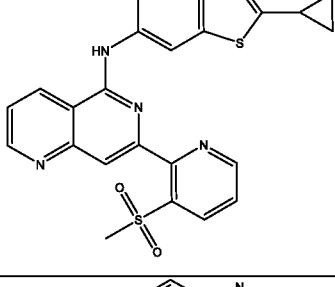
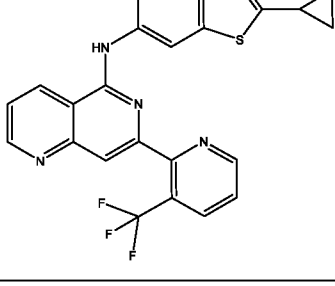
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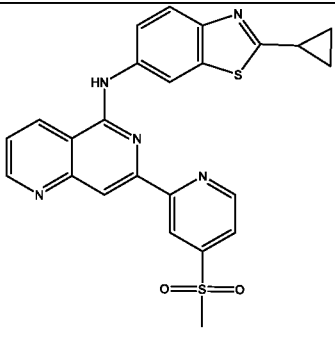
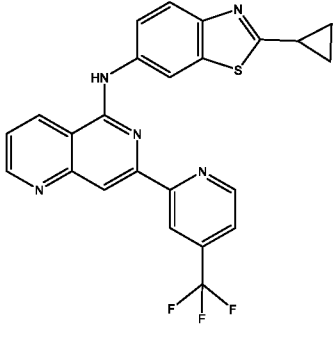
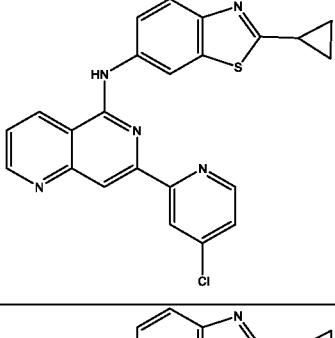
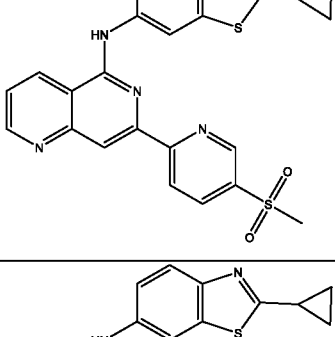
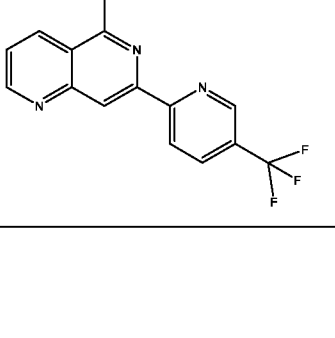
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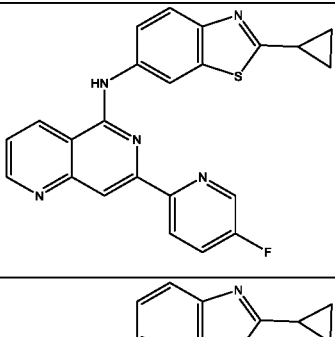
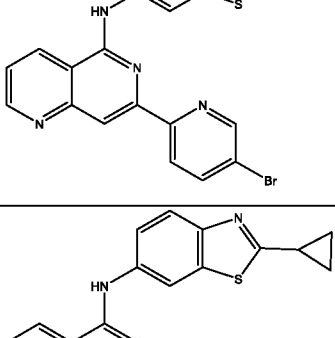
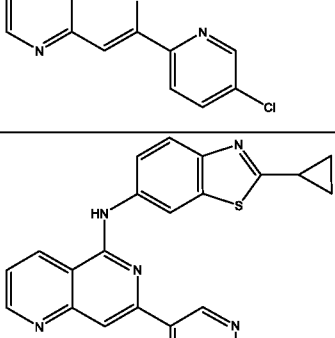
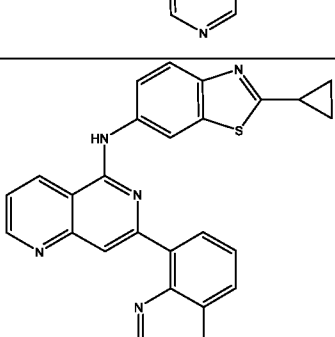
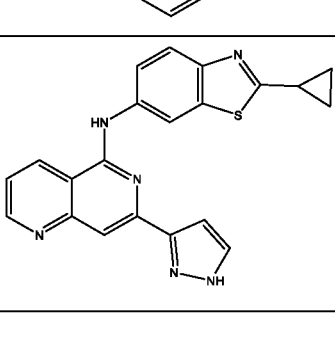
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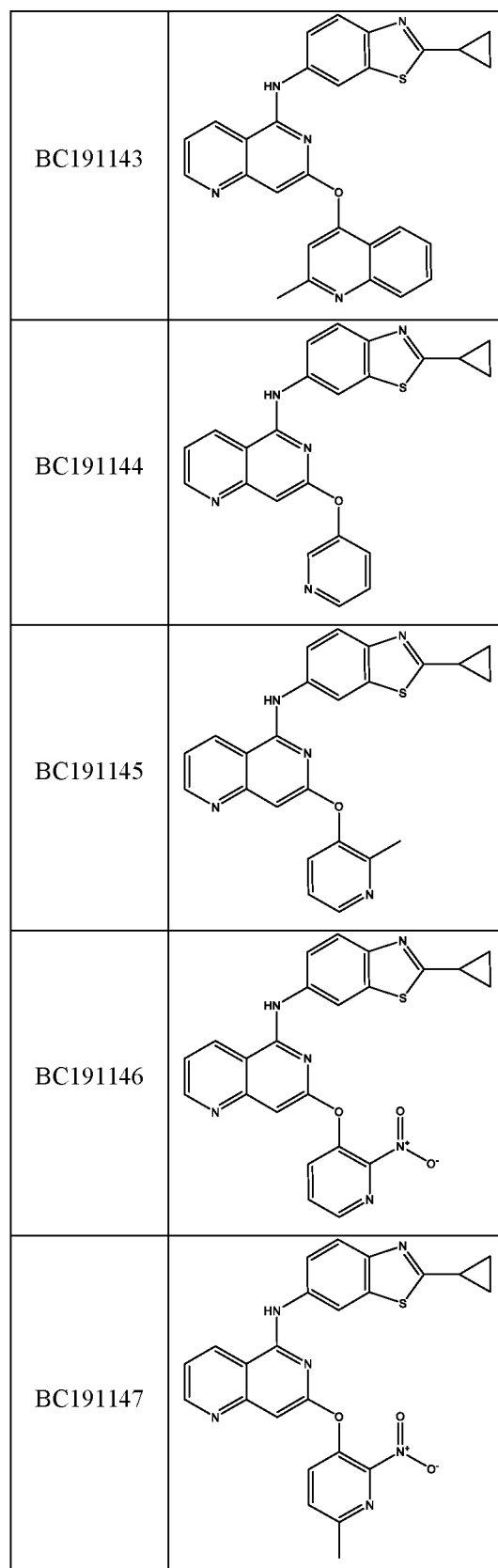
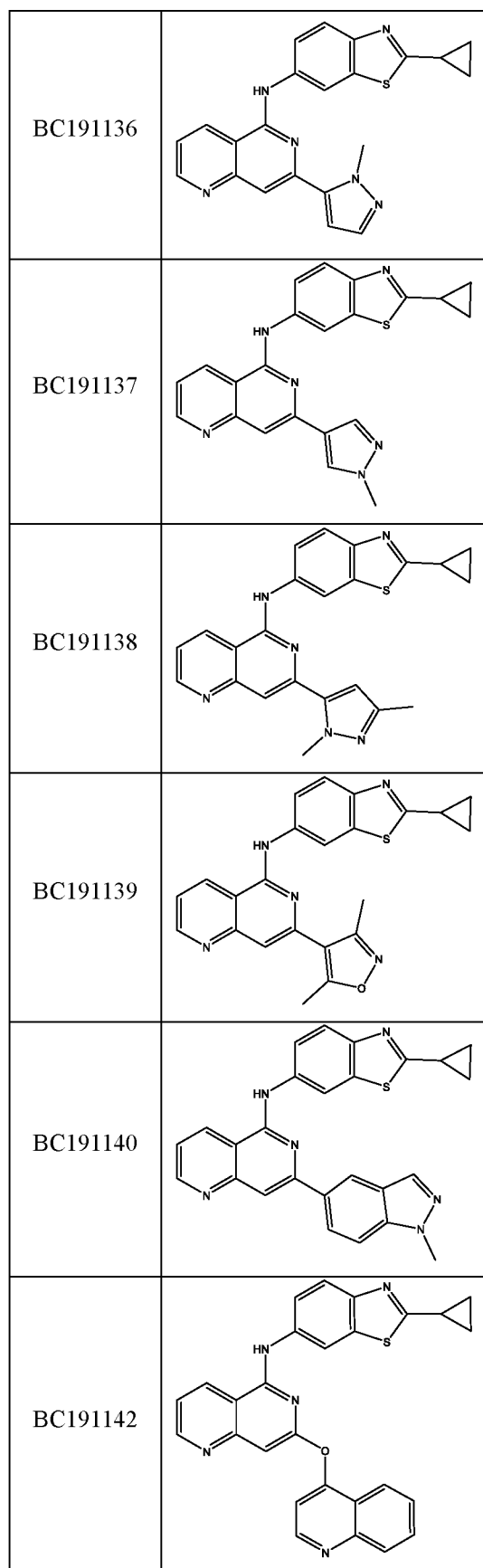
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or a pharmaceutically acceptable salt thereof.

91. The compound of claim 84, wherein the compound of Formula (IIb) is selected from:

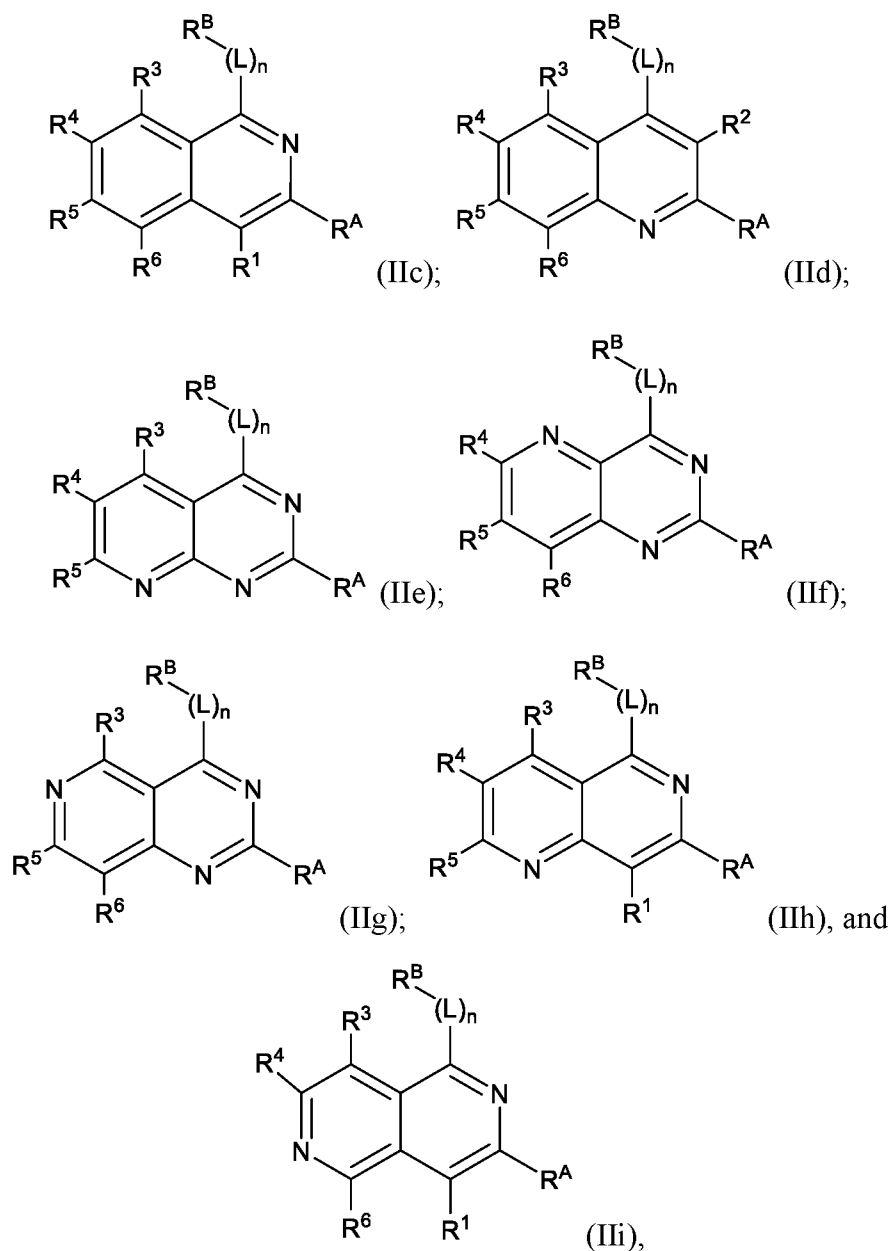
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or a pharmaceutically acceptable salt thereof.

92. A compound selected from any one of the following Formulae (IIc)-(Ili):



or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from O, S, S(=O)₂, C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO₂, OH, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

each R^N is independently selected from H and C₁₋₆ alkyl, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo,

CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1},
NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1};

n is an integer selected from 1, 2, and 3;

each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from H, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and N(R^N)-Cy^{A1};

Cy^{A1} is selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and Cy¹, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1};

or, when R^B is attached to L which is N(R^N), R^B and R^N together with the N atom to which they are attached form 4-14 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{al}, C(O)R^{b1}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{b1}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{b1}, S(O)₂R^{b1}, and S(O)₂NR^{cl}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₄ cycloalkyl, 5-10 membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2};

R^{Cy1} and R^{Cy2} are each independently selected from oxo, halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

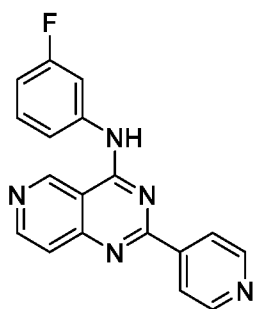
each Cy^2 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkylene, C_{3-10} cycloalkyl- C_{1-4} alkylene, (5-10 membered heteroaryl)- C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)- C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkylene, C_{3-10} cycloalkyl- C_{1-4} alkylene, (5-10 membered heteroaryl)- C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)- C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g ;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g ;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g ; and

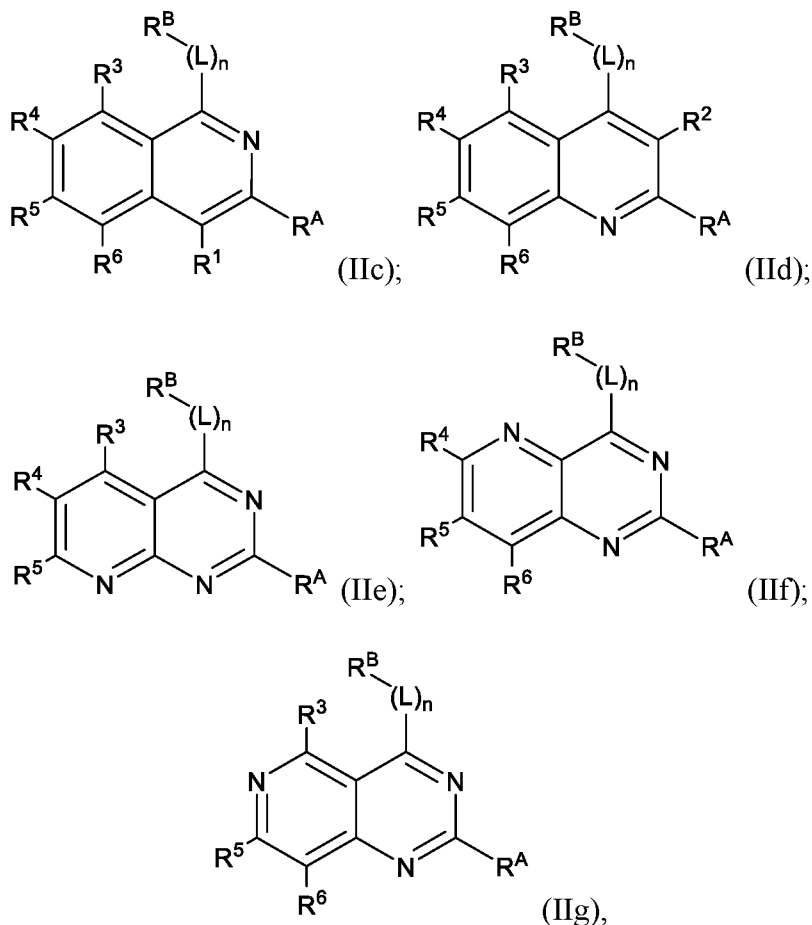
each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino, provided that the compound is not:



93. The compound of claim 92, wherein R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{bl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, NO₂, OR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}S(O)₂R^{bl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}; and each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2}.

94. The compound of claim 92 or 93, selected from any one of the following

Formulae (IIc)-(IIg):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1} ; and

R^{Cy1} and R^{Cy2} are each independently selected from halo, CN, NO_2 , Cy^2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^2 , halo, CN, NO_2 , OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

95. The compound of any one of claims 92-94, wherein:

n is 1;

L is selected from C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with OH;

R^N is selected from H and C₁₋₆ alkyl;

R¹, R², R³, R⁴, R⁵, and R⁶ are each independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1};

R^A is selected from Cy^{A1}, O-Cy^{A1}, and NH-Cy^{A1};

each Cy^{A1} is selected from C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

R^B is selected from C₁₋₆ alkyl and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, CN, OR^{a1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

or, when R^B is attached to N(R^N), R^B and R^N together with the N atom to which they are attached form 4-14 membered heterocycloalkyl, which is optionally substituted with Cy¹, C₁₋₆ alkyl, OR^{a1}, and halo;

each R^{Cy1} is independently selected from halo, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, and S(O)₂R^{b2}, wherein said C₁₋₆ alkyl is optionally substituted with OR^{a2};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₄ cycloalkyl, 5-10 membered heteroaryl, and 4-14 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2};

each R^{Cy2} is independently selected from halo, Cy², C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR^{a2}, C(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, and S(O)₂R^{b2}; and

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H and C₁₋₆ alkyl.

96. The compound of any one of claims 92-94, wherein:

n is 1;

L is selected from C₁₋₃ alkylene, C(=O), and N(R^N), wherein said C₁₋₃ alkylene is optionally substituted with OH;

R^N is selected from H and C₁₋₆ alkyl;

R¹, R², R³, R⁴, R⁵, and R⁶ are each independently selected from H, halo, CN, C₁₋₆ alkyl, OR^{a1}, NR^{c1}R^{d1}, and S(O)₂R^{b1};

R^A is selected from Cy^{A1} , $O-Cy^{A1}$, and $NH-Cy^{A1}$;

each Cy^{A1} is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or, when R^B is attached to L which is $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)OR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, and $S(O)_2R^{b2}$, wherein said C_{1-6} alkyl is optionally substituted with OR^{a2} ;

each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

97. The compound of any one of claims 92-94, wherein:

n is 1;

L is selected from C_{1-3} alkylene, $C(=O)$, and $N(R^N)$, wherein said C_{1-3} alkylene is optionally substituted with OH;

R^N is selected from H and C_{1-6} alkyl;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and OR^{a1} ;

R^A is selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1} ;

R^B is selected from C_{1-6} alkyl and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, OR^{a1} , $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

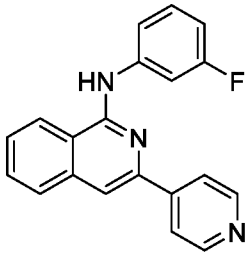
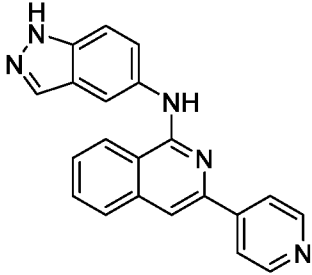
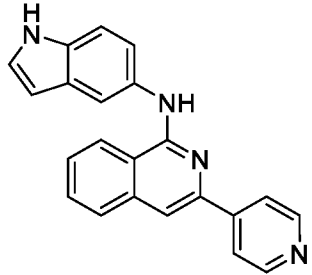
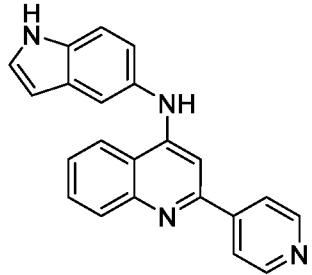
or, when R^B is attached to L which is $N(R^N)$, R^B and R^N together with the N atom to which they are attached form 4-7 membered heterocycloalkyl, which is optionally substituted with OR^{a1} ;

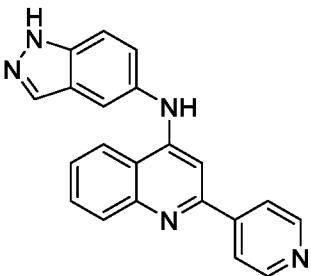
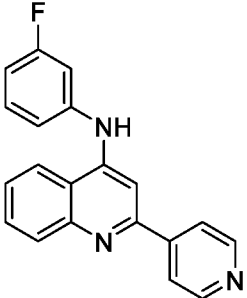
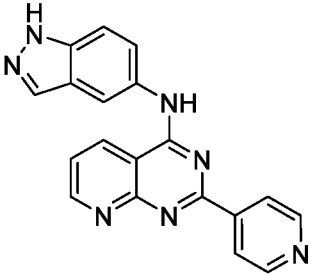
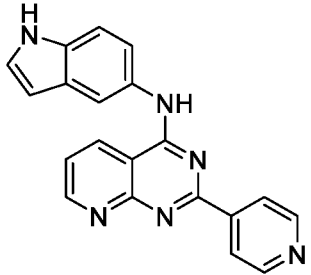
each R^{Cy1} is independently selected from halo, NO_2 , C_{1-6} alkyl, OR^{a2} , and $C(O)OR^{a2}$,

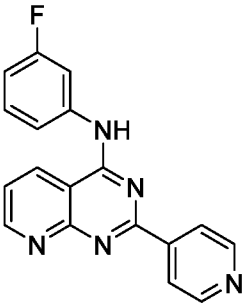
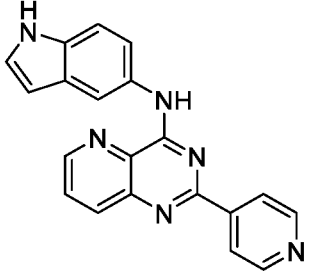
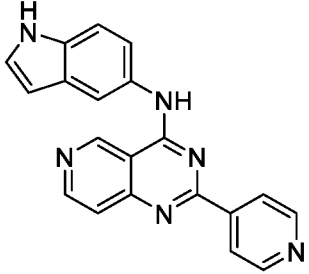
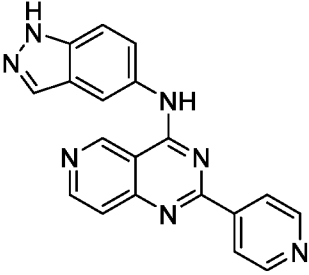
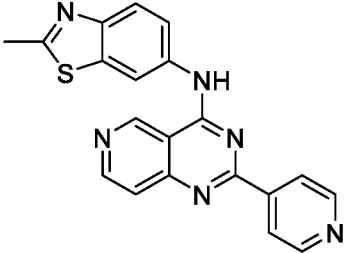
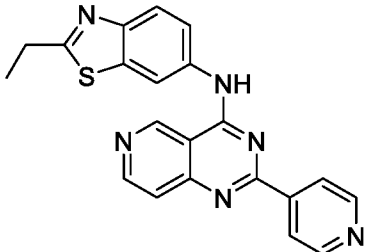
each R^{Cy2} is independently selected from halo, CN, C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $NR^{c2}R^{d2}$; and

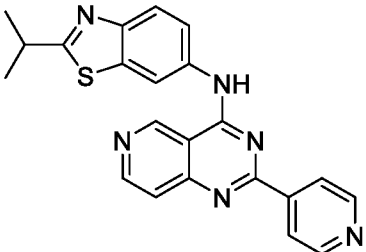
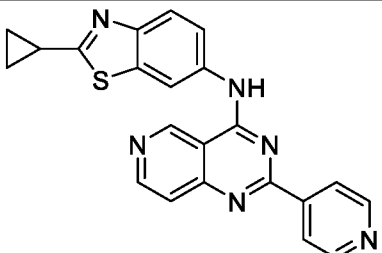
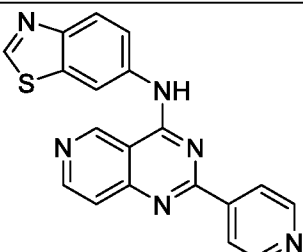
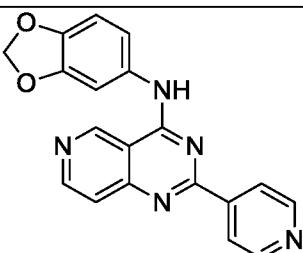
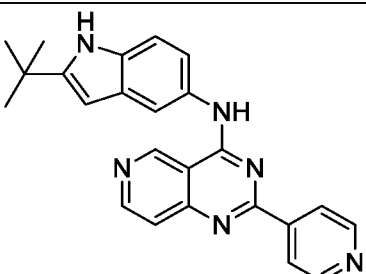
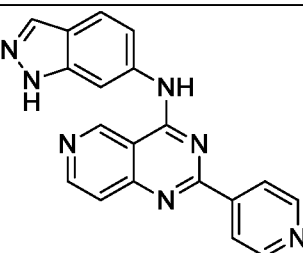
each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H and C_{1-6} alkyl.

98. The compound of claim 92, wherein the compound is selected from any one of the following compounds:

BC18663	
BC18668	
BC18669	
BC18687	

BC18688	
BC18689	
BC18707	
BC18708	

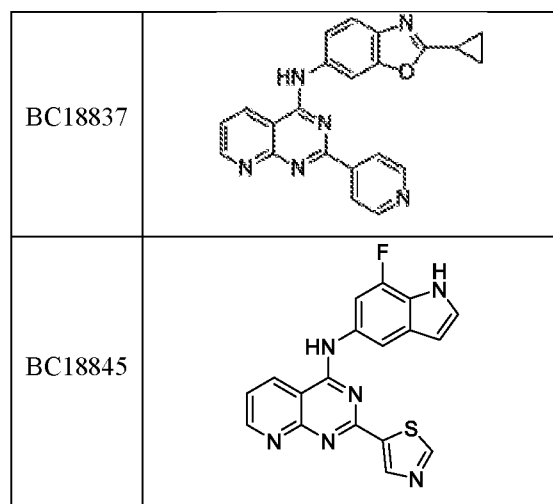
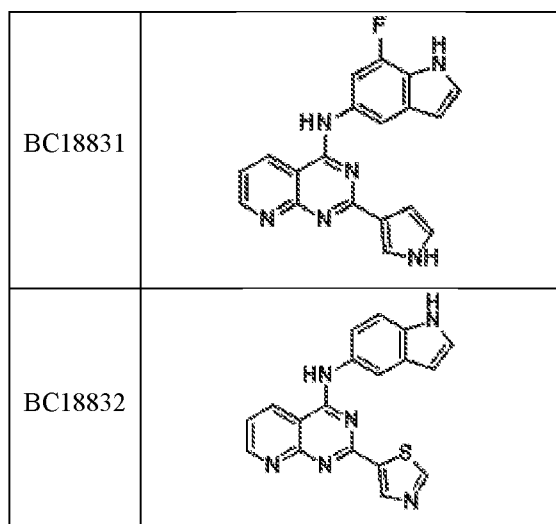
BC18709	
BC18711	
BC18713	
BC18714	
BC18755	
BC18756	

BC18757	
BC18758	
BC18759	
BC18760	
BC18761	
BC18762	

BC18763	
BC18764	
BC18765	
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BC18770	
BC18771	
BC18772	
BC18773	
BC18774	

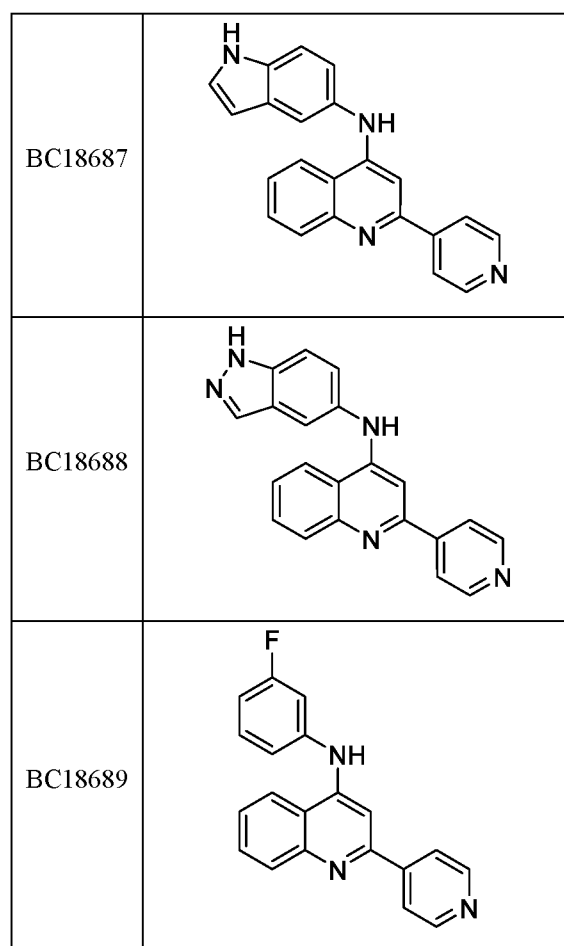
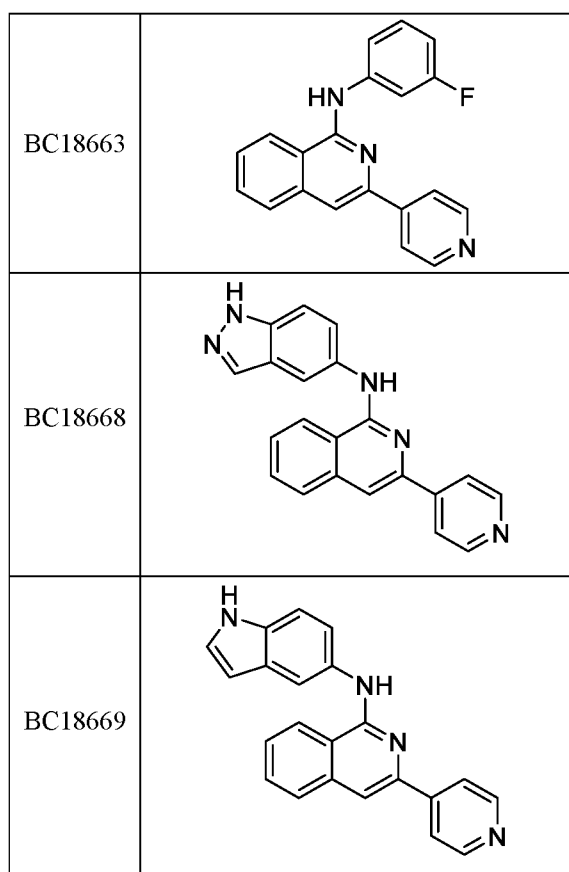
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BC18778	
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BC18785	
BC18796	

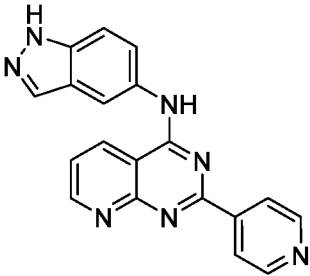
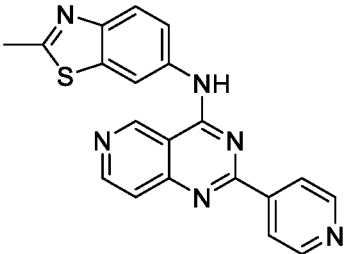
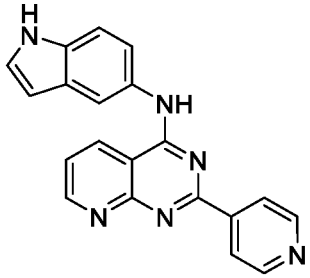
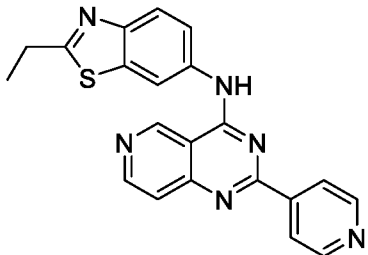
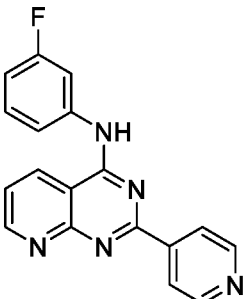
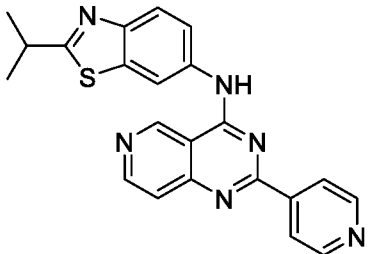
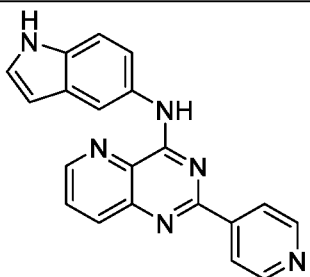
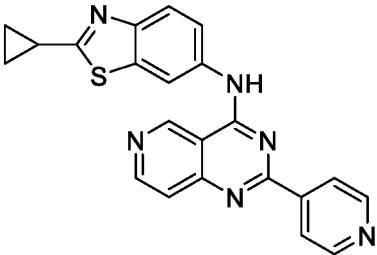
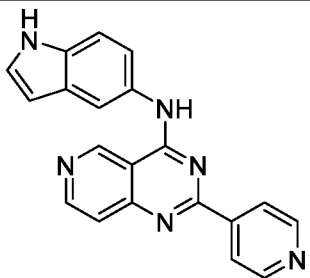
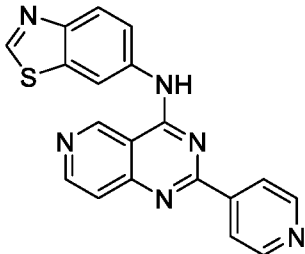
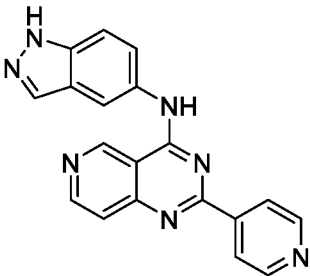
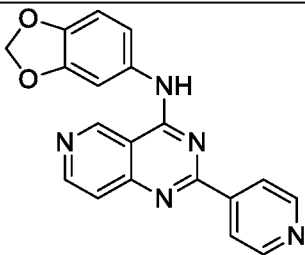
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BC18806	
BC18808	
BC18821	
BC18829	
BC18830	

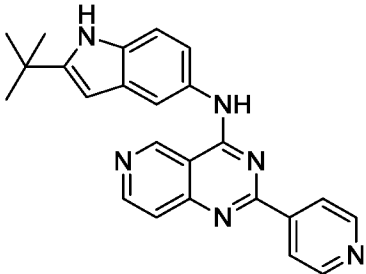
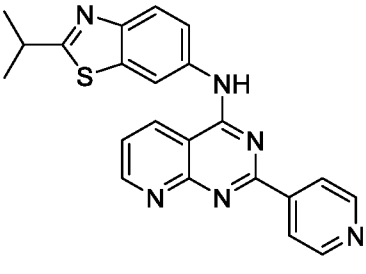
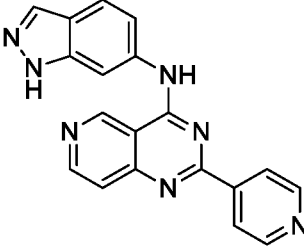
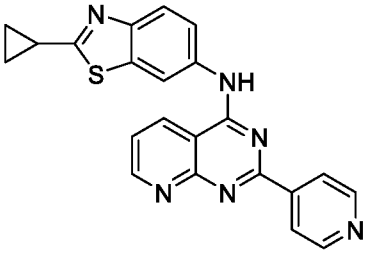
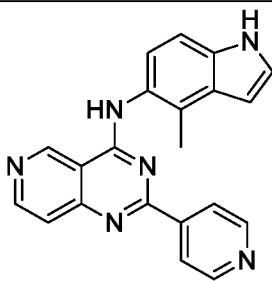
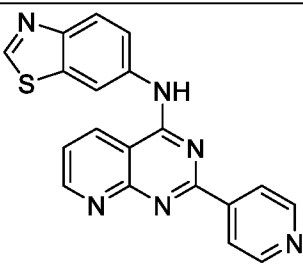
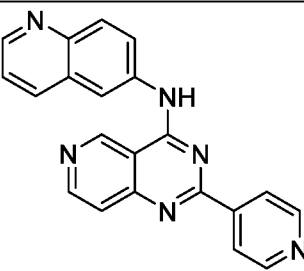
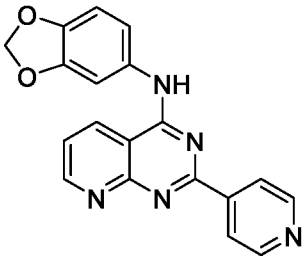
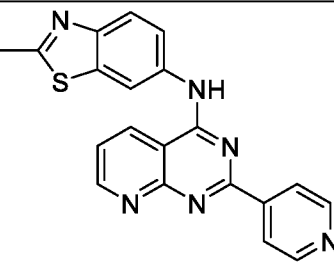
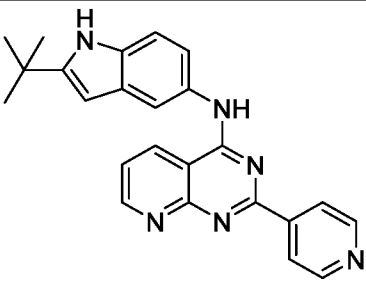
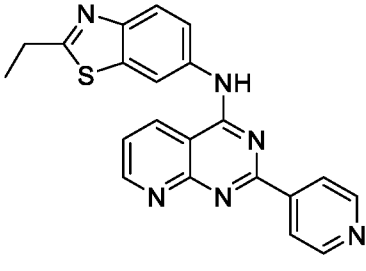
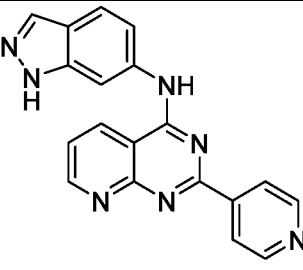


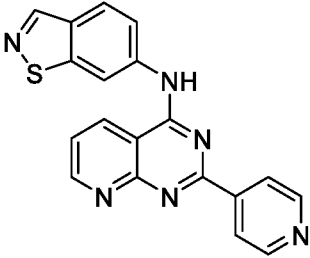
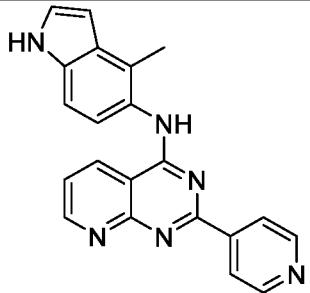
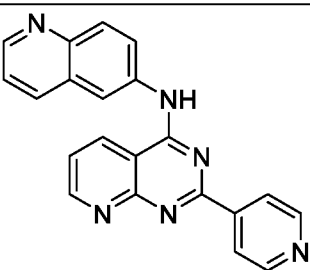
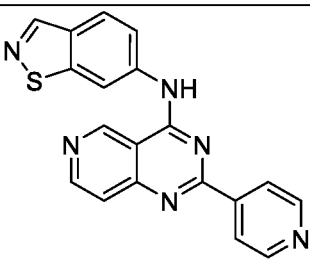
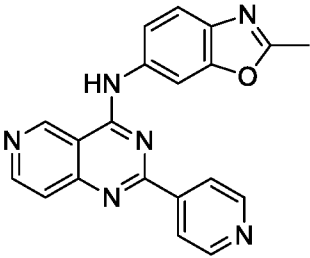
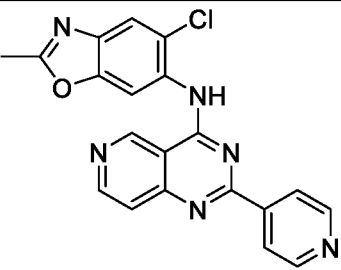
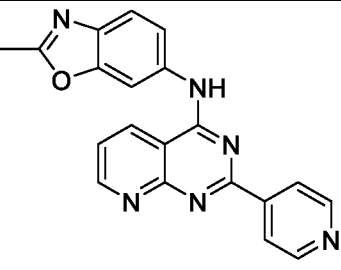
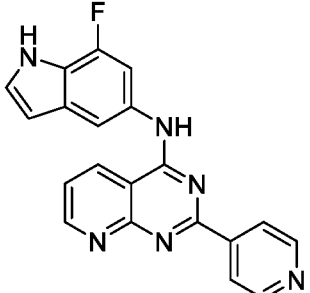
or a pharmaceutically acceptable salt thereof.

99. The compound of claim 92, wherein the compound is selected from any one of the following compounds:



BC18707		BC18755	
BC18708		BC18756	
BC18709		BC18757	
BC18711		BC18758	
BC18713		BC18759	
BC18714		BC18760	

BC18761		BC18767	
BC18762		BC18768	
BC18763		BC18769	
BC18764		BC18770	
BC18765		BC18771	
BC18766		BC18772	

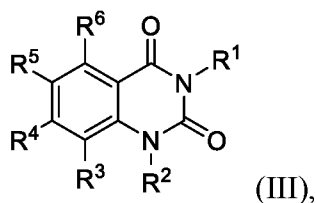
BC18773	
BC18774	
BC18775	
BC18776	
BC18778	
BC18783	
BC18785	
BC18796	

or a pharmaceutically acceptable salt thereof.

100. The compound of claim 92, wherein the compound is selected from any one of the compounds of Table 5, Table 5a, or Table 6, or a pharmaceutically acceptable salt thereof.

101. The compound of claim 92, wherein the compound is selected from any one of the compounds of Table 5 or Table 6, or a pharmaceutically acceptable salt thereof.

102. A method for increasing TFEB polypeptide levels within a nucleus of a cell within a mammal, wherein said method comprises administering, to said mammal, a compound of Formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1 , wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^3 , R^4 , R^5 , and R^6 are each independently selected from H, halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from CN, NO_2 , OR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy2} ;

each R^{Cy2} is independently selected from halo, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}S(O)_2R^{b2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2,

or 3 substituents independently selected from halo, CN, NO₂, OR^{a2}, and C(O)R^{b2}, C(O)NR^{c2}R^{d2},

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, cyano-C₁₋₃ alkylene, HO-C₁₋₃ alkylene, C₆₋₁₀ aryl, C₆₋₁₀ aryloxy, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkylene, C₃₋₁₀ cycloalkyl-C₁₋₄ alkylene, (5-10 membered heteroaryl)-C₁₋₄ alkylene, (4-10 membered heterocycloalkyl)-C₁₋₄ alkylene, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

103. The method of claim 102, wherein R¹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, and Cy¹, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹.

104. The method of claim 102 or 103, wherein R^2 is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$.
105. The method of any one of claims 102-104, wherein R^3 , R^4 , R^5 , and R^6 are each independently selected from H and $C(O)NR^{c1}R^{d1}$.
106. The method of claim 105, wherein R^3 and R^6 are each H.
107. The method of claim 106, wherein R^4 is $C(O)NR^{c1}R^{d1}$.
108. The method of claim 106, wherein R^5 is $C(O)NR^{c1}R^{d1}$.
109. The method of any one of claims 102-108, wherein each Cy^1 is independently selected from C_{6-10} aryl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2} .
110. The method of any one of claims 102-109, wherein each R^{Cy2} is independently selected from halo, CN, C_{1-6} alkyl, and OR^{a2} ; wherein said C_{1-6} alkyl is optionally substituted with $C(O)NR^{c2}R^{d2}$.
111. The method of any one of claims 102-110, wherein each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{6-10} aryl- C_{1-4} alkylene, and (5-10 membered heteroaryl)- C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{6-10} aryl- C_{1-4} alkylene, and (5-10 membered heteroaryl)- C_{1-4} alkylene, are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g .
112. The method of any one of claims 102-111, wherein each R^g is independently selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy.
113. The method of claim 102, wherein:
 R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, and Cy^1 , wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 ;
 R^2 is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$;
 R^3 , R^4 , R^5 , and R^6 are each independently selected from H and $C(O)NR^{c1}R^{d1}$;

Cy¹ is independently selected from C₆₋₁₀ aryl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy2};

R^{Cy2} is independently selected from halo, CN, C₁₋₆ alkyl, and OR^{a2}; wherein said C₁₋₆ alkyl is optionally substituted with C(O)NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl-C₁₋₄ alkylene, and (5-10 membered heteroaryl)-C₁₋₄ alkylene, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₆₋₁₀ aryl-C₁₋₄ alkylene, and (5-10 membered heteroaryl)-C₁₋₄ alkylene are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from halo, C₁₋₆ alkyl, and C₁₋₆ alkoxy.

114. The method of claim 102, wherein the compound is selected from any one of the compounds in Table 4, or a pharmaceutically acceptable salt thereof.

115. The method of any one of claims 102-114, wherein said mammal is a human.

116. A pharmaceutical composition comprising a compound as recited in any one of claims 102-114, or a pharmaceutically acceptable salt thereof, and a pharmaceutically available carrier.

117. A method of treating a mammal having a disease, disorder, or condition responsive to an increase in TFEB polypeptide levels within a nucleus of a cell, wherein said method comprises administering, to said mammal, (a) a compound of Formula (I) as recited in any one of claims 1-67, or a pharmaceutically acceptable salt thereof, (b) a pharmaceutical composition as recited in claim 69 or 70, (c) a compound as recited in any one of claims 71-114, or a pharmaceutically acceptable salt thereof, or (d) a pharmaceutical composition as recited in claim 116.

118. The method of claim 117, wherein said mammal is a human.

119. The method of any one of claims 117-118, wherein said method comprises treating a mammal having a lysosomal storage disease (LSD).

120. The method of claim 119, wherein said LSD is selected from the group consisting of Krabbe disease, Sanfilippo syndrome, multiple sulfatase deficiency,

alpha-mannosidosis, Fabry disease, Hunter syndrome, Scheie syndrome, Sanfilippo syndrome, Maroteaux–Lamy syndrome, hyaluronidase deficiency, sialidosis, mucopolidin 1 deficiency, neuronal ceroid lipofuscinoses (Batten Disease), mucopolysaccharidoses Type I, II, III, IV, VI, VII, and IX, Hurler–Scheie syndrome, Morquio syndrome, glycoproteinosis, multiple sulfatase deficiency, glycogen storage disease, metachromatic Leukodystrophy, Sly syndrome, I-cell disease, Danon disease, Niemann-Pick disease type A, B, C1 and C2, Sandhoff disease, lysosomal acid lipase deficiency, GM2 gangliosidoses, Tay–Sachs disease, Gaucher disease, Salla disease, Pompe disease, Danon disease, cholesteryl ester storage disease, aspartylglucosaminuria, cystinosis, mucopolidosis type I-IV, Schindler disease type I and II, Wolman disease, fucosidosis, pycnodysostosis and free sialic acid storage disease.

121. The method of any one of claims 117-118, wherein said method comprises treating a mammal having an acute or chronic inflammation disorder.
122. The method of claim 121, wherein said acute or chronic inflammation disorder is selected from the group consisting of asthma, chronic obstructive lung disease, pulmonary fibrosis, pneumonitis (e.g., hypersensitivity pneumonitis or radiation pneumonitis), pneumonia, cystic fibrosis, psoriasis, arthritis/rheumatoid arthritis, rhinitis, pharyngitis, cystitis, prostatitis, dermatitis, allergy including hayfever, nephritis, conjunctivitis, encephalitis, meningitis, ophthalmitis, uveitis, pleuritis, pericarditis, myocarditis, atherosclerosis, human immunodeficiency virus related inflammation, diabetes, osteoarthritis, psoriatic arthritis, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), colitis, sepsis, vasculitis, bursitis, connective tissue disease, autoimmune diseases (e.g., systemic lupus erythematosus (SLE)), polymyalgia rheumatica, scleroderma, Wegener's granulomatosis, temporal arteritis, vasculitis, cryoglobulinemia, multiple sclerosis, viral or influenza-induced inflammation, chronic bacterial colonization or persistent intracellular pathogen, and impaired responsiveness to antigenic challenge or vaccines administration.
123. The method of any one of claims 117-118, wherein said method comprises treating a mammal having an age-related disorder.

124. The method of claim 123, wherein said age-related disorder is selected from the group consisting of neurodegenerative diseases, metabolic diseases, metabolic syndrome, NASH, fatty liver, diabetes, sarcopenia, frailty, age-related wet and dry macular degeneration, inherited or acquired retinal degenerative diseases, age-related hearing loss, early or late cognitive decline, early or late cognitive impairment, osteoporosis, age-related organ dysfunction, and age-related immune dysfunctions.
125. The method of any one of claims 117-118, wherein said method comprises treating a mammal having Alzheimer's disease, ALS, Huntington's disease, Parkinson's disease, primary age-related tauopathy, progressive supranuclear palsy, frontotemporal dementia, chronic traumatic encephalopathy, or traumatic brain injury.
126. The method of any one of claims 117-118, wherein said method comprises treating a mammal having an inherited or acquired disease of muscle.
127. The method of claim 126, wherein the inherited or acquired disease of muscle is selected from the group consisting of myofibrillar myopathy, sporadic inclusion body myositis, inclusion body myopathy with frontotemporal dementia (IBMFTD), and cardiomyopathy.

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NLIERRRFNINDRIKELGMLIPKANDLDVRWNKGTLKASVDYIRRMQKDLQKSRELEN
HSRREMTNKKQLWLRIQELEMQARVHGLPTTSPSGMNMALAQQVVKQLPSEEGPGEAL
MIGAFVDPDFPIPALPPOAPLPLPTOPPSPFHHLDFSHLSFGGREDEGPPGYPEPLAPG

(SEQ ID NO:1)

FIG. 1

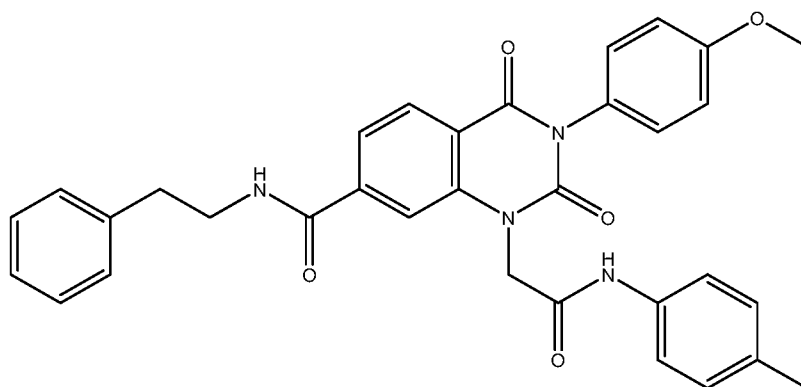


FIG. 2A

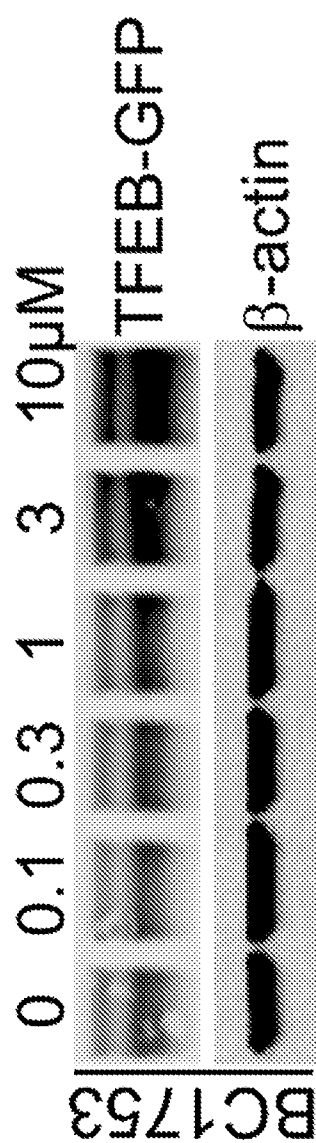


FIG. 2B

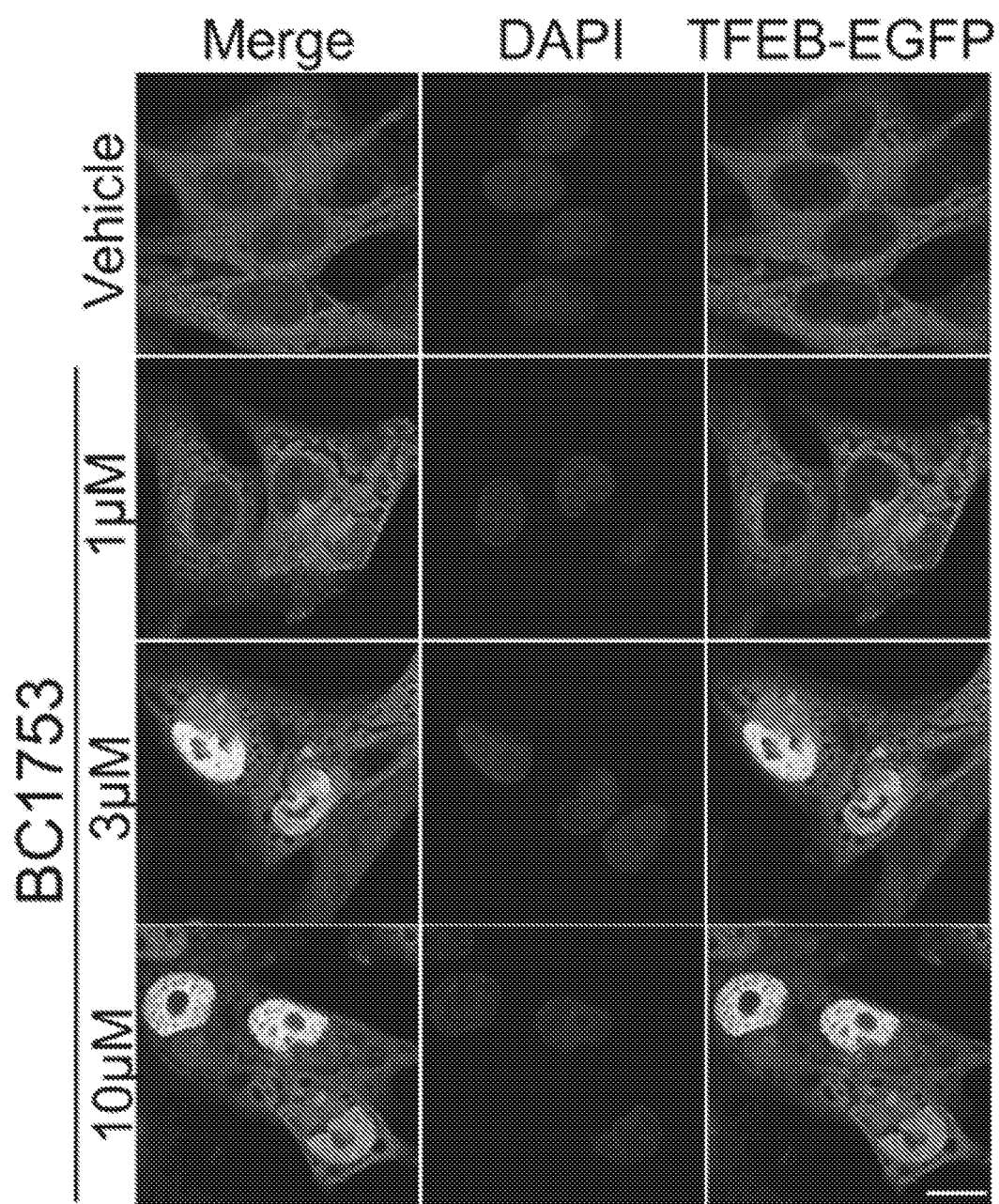


FIG. 2C

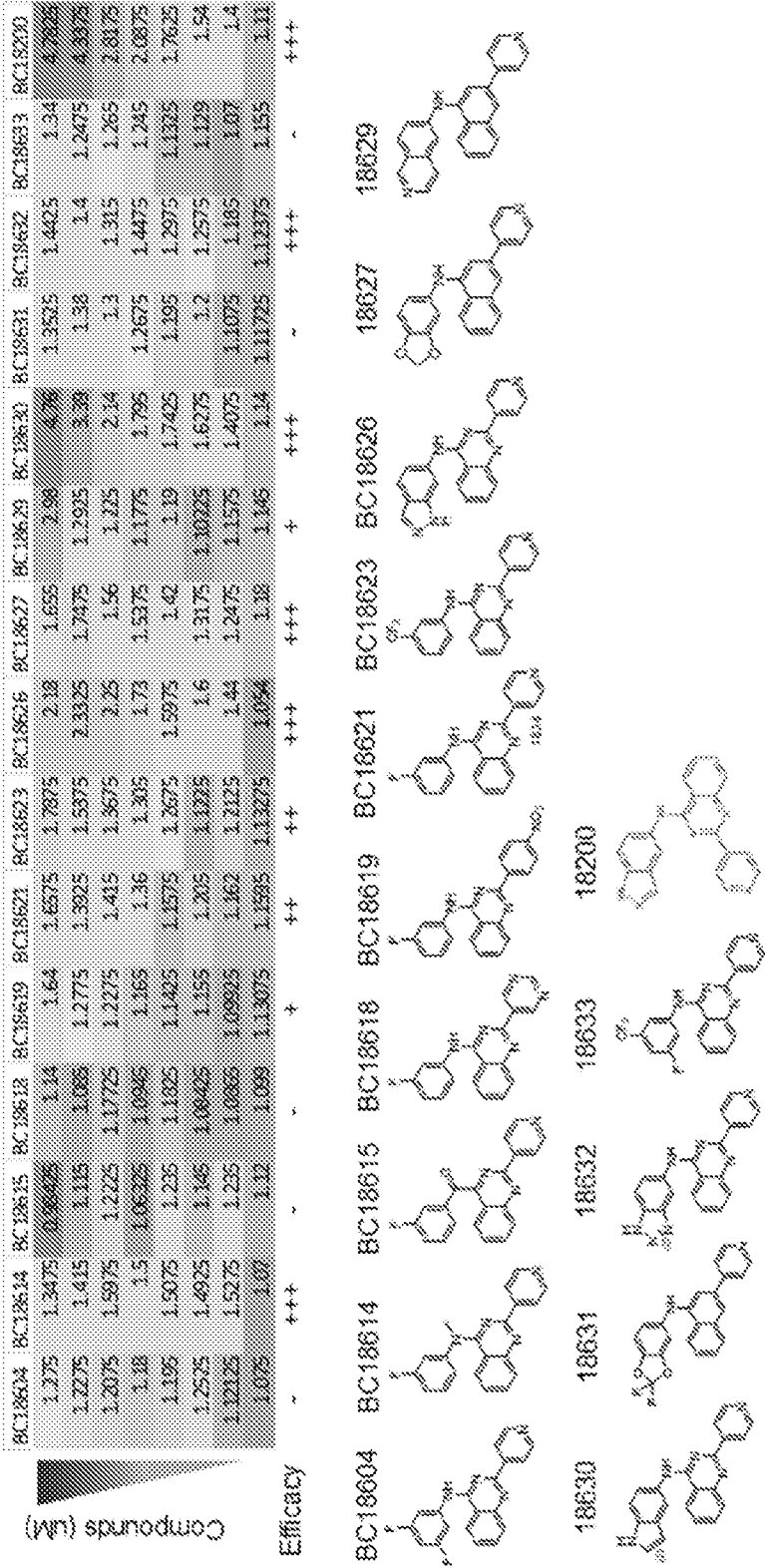


FIG. 3

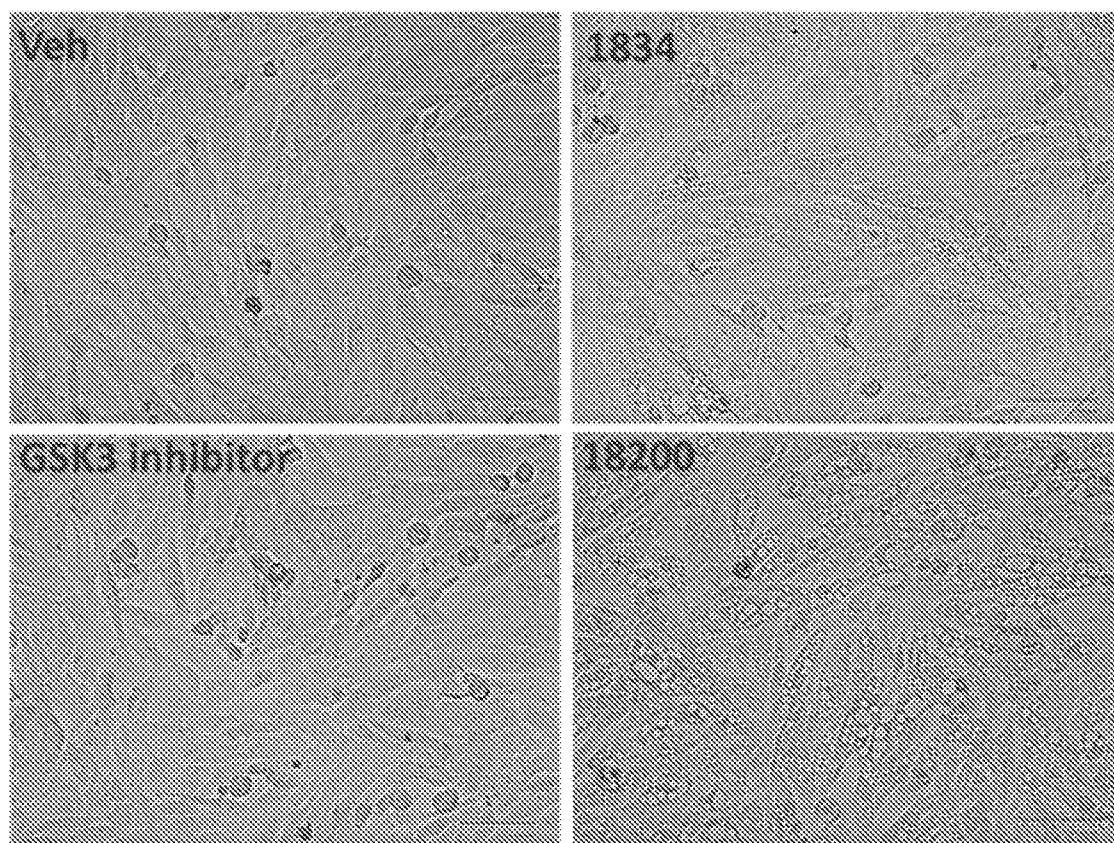
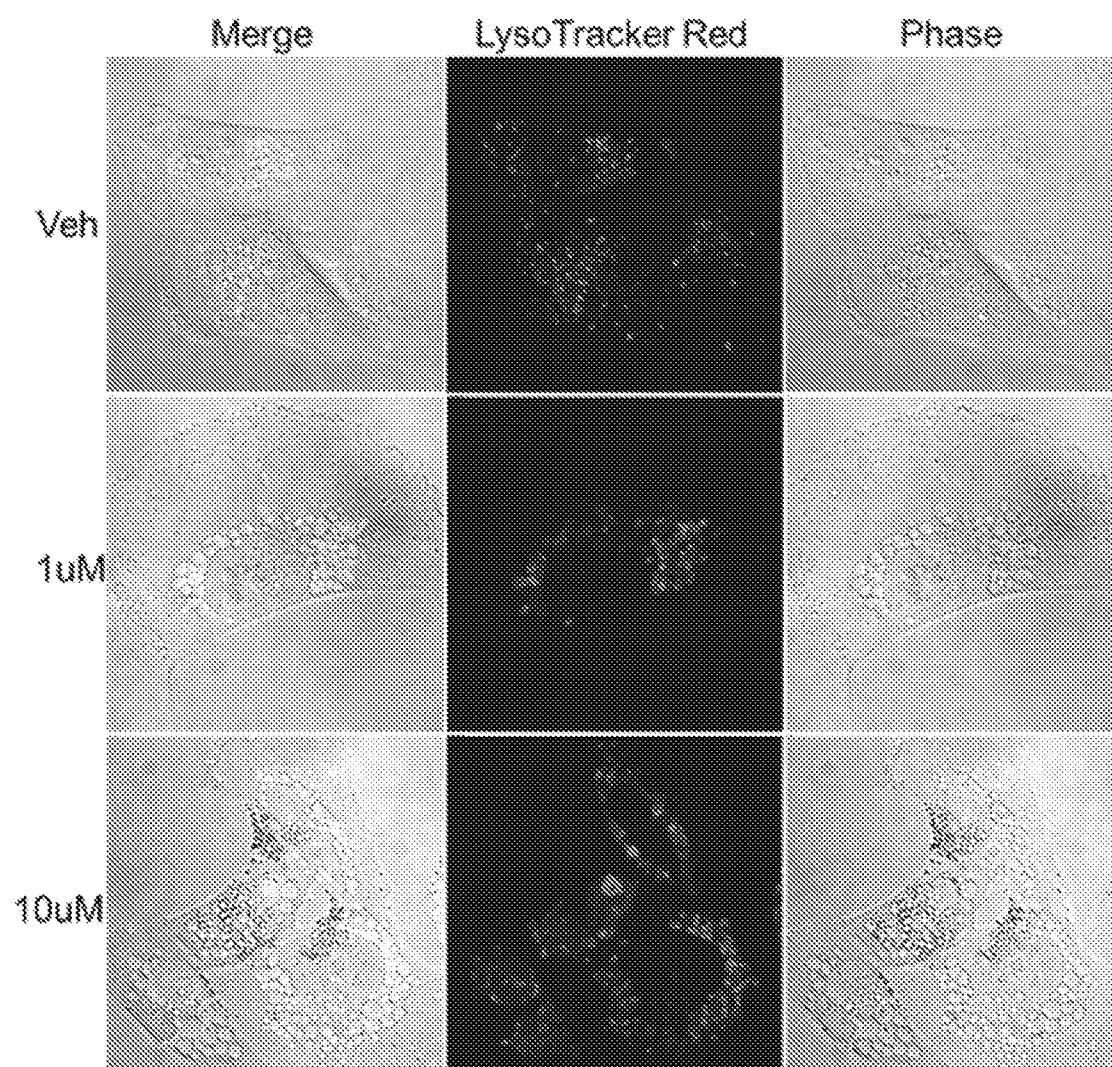


FIG. 4A

**FIG. 4B**

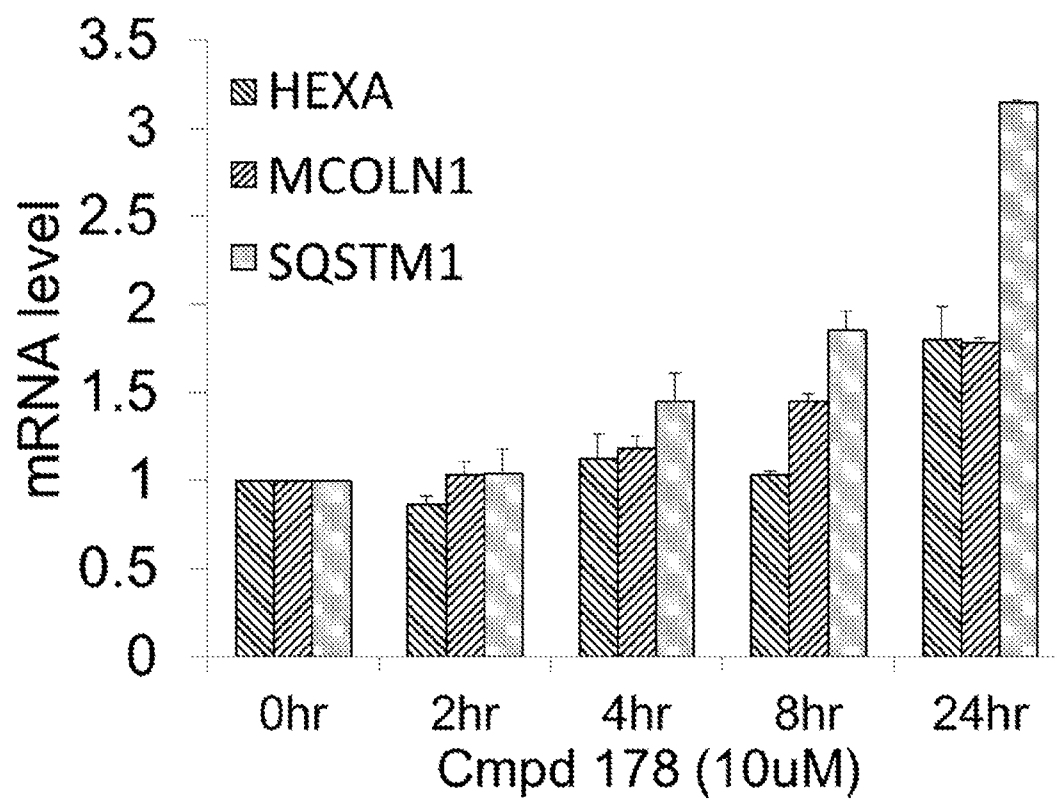


FIG. 5A

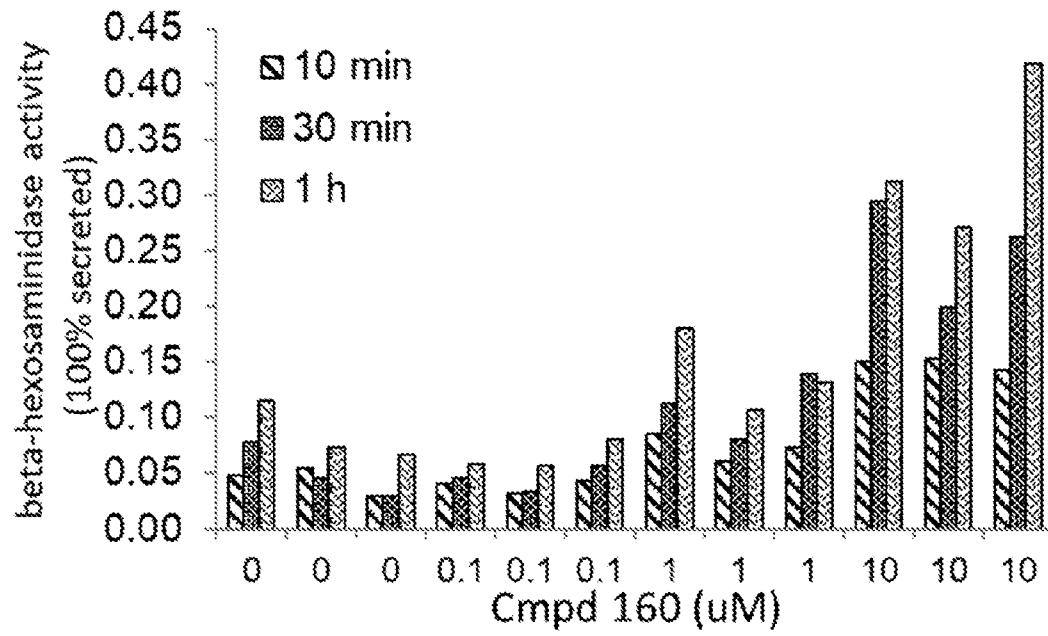


FIG. 5B

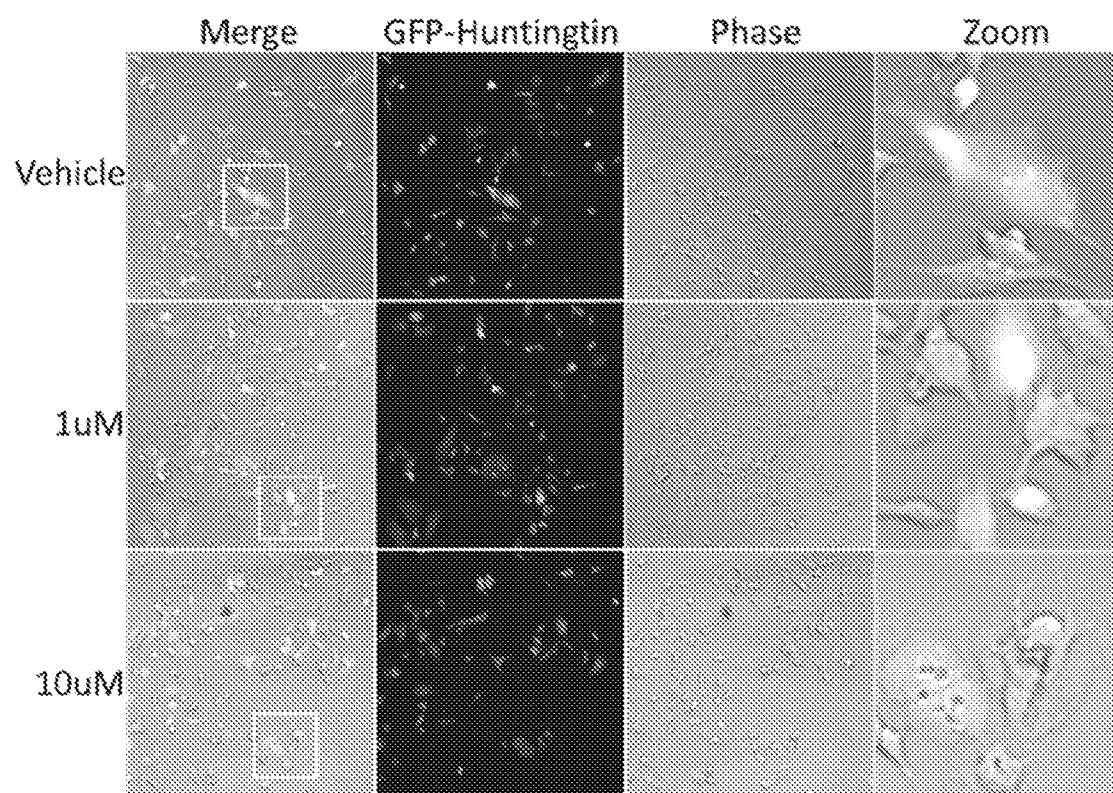


FIG. 6A

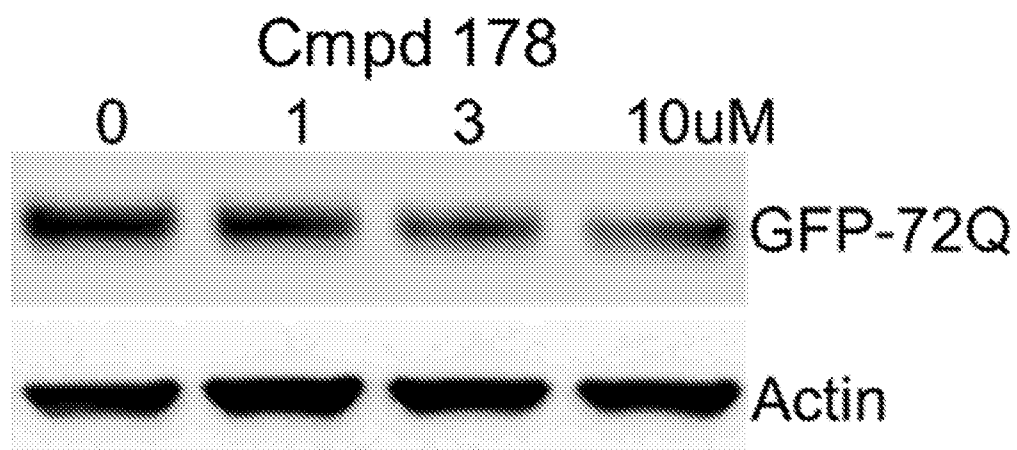
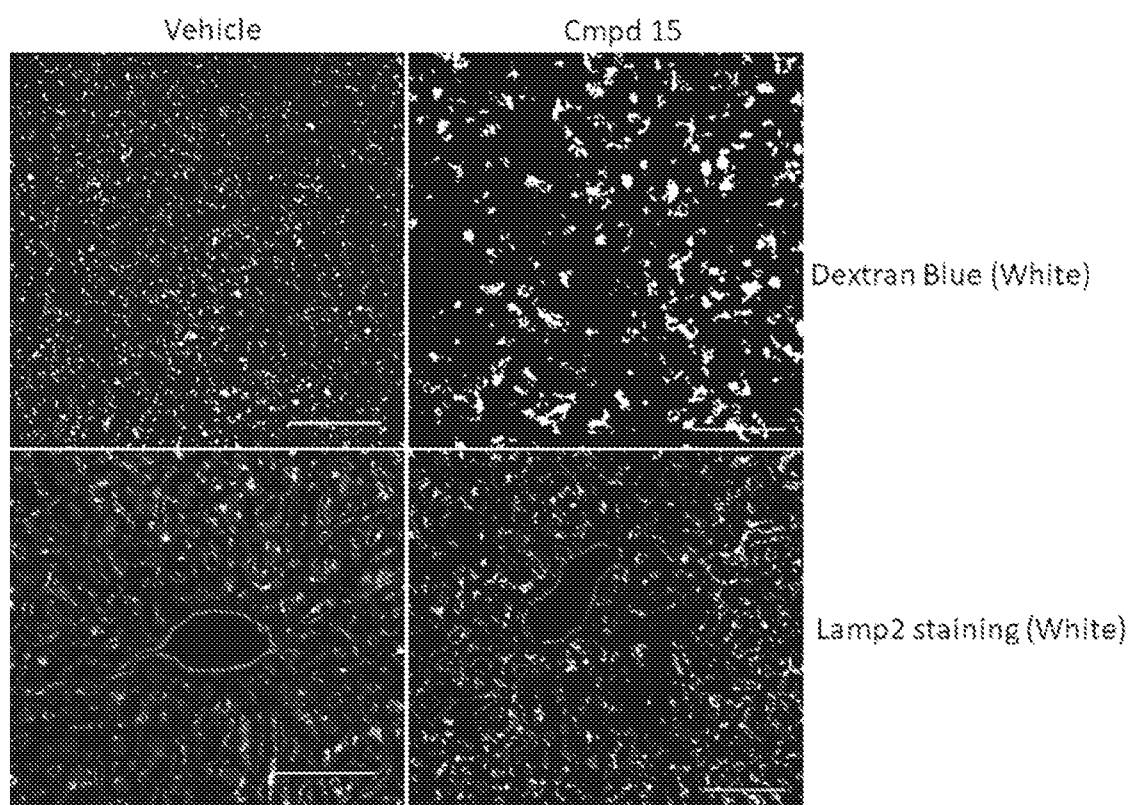


FIG. 6B

**FIG. 7**