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(54) **METHODS OF REGULATING BCL11A EXPRESSION AND TREATMENT OF BCL11A-MEDIATED DISORDERS**

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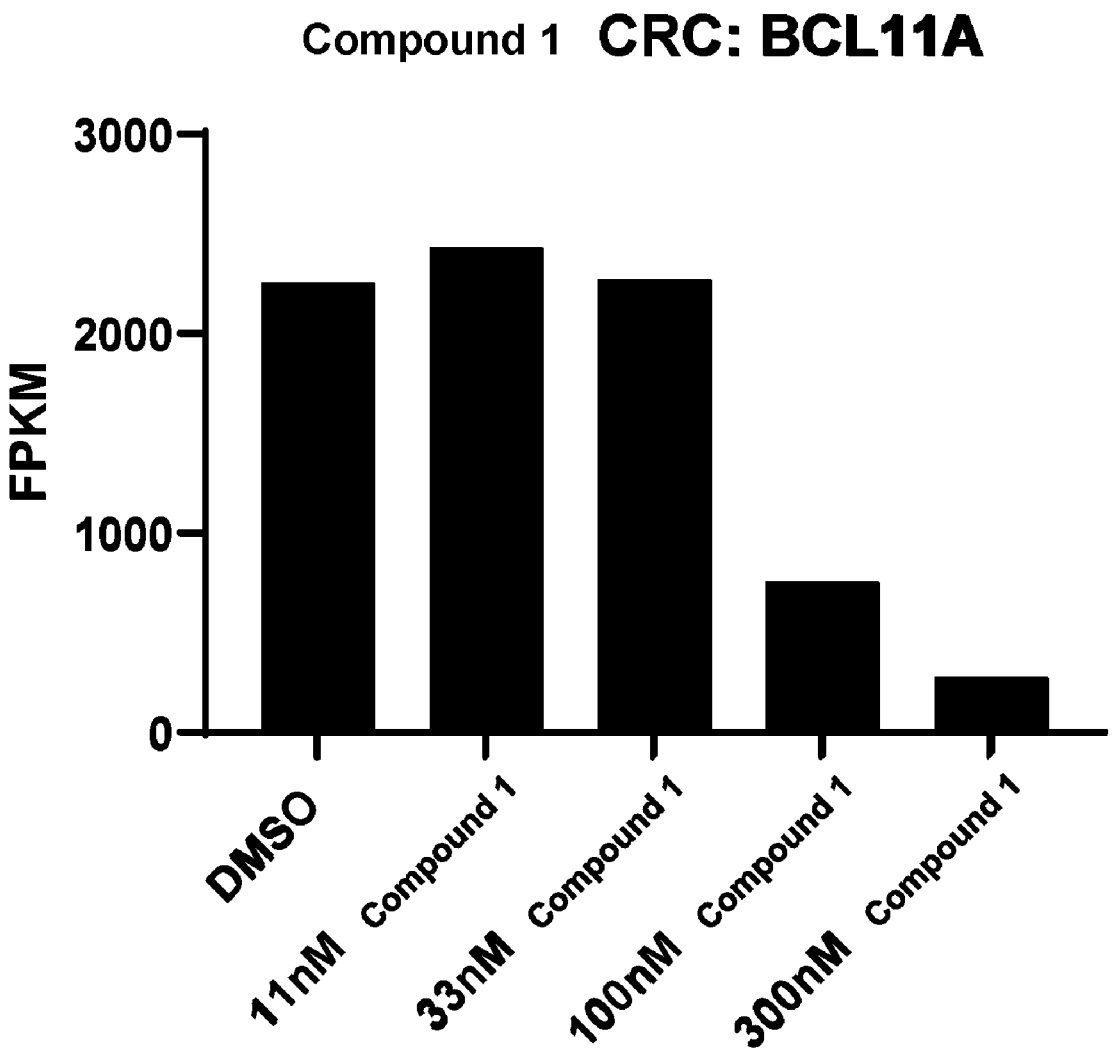
(57) **ABSTRACT**

Provided herein, in part, are methods of downregulating BCL11A expression and treatment of BCL11A mediated disorders. The methods may comprise the use of inhibitors such as EED, EHZ2, and/or PRC2 inhibitors.



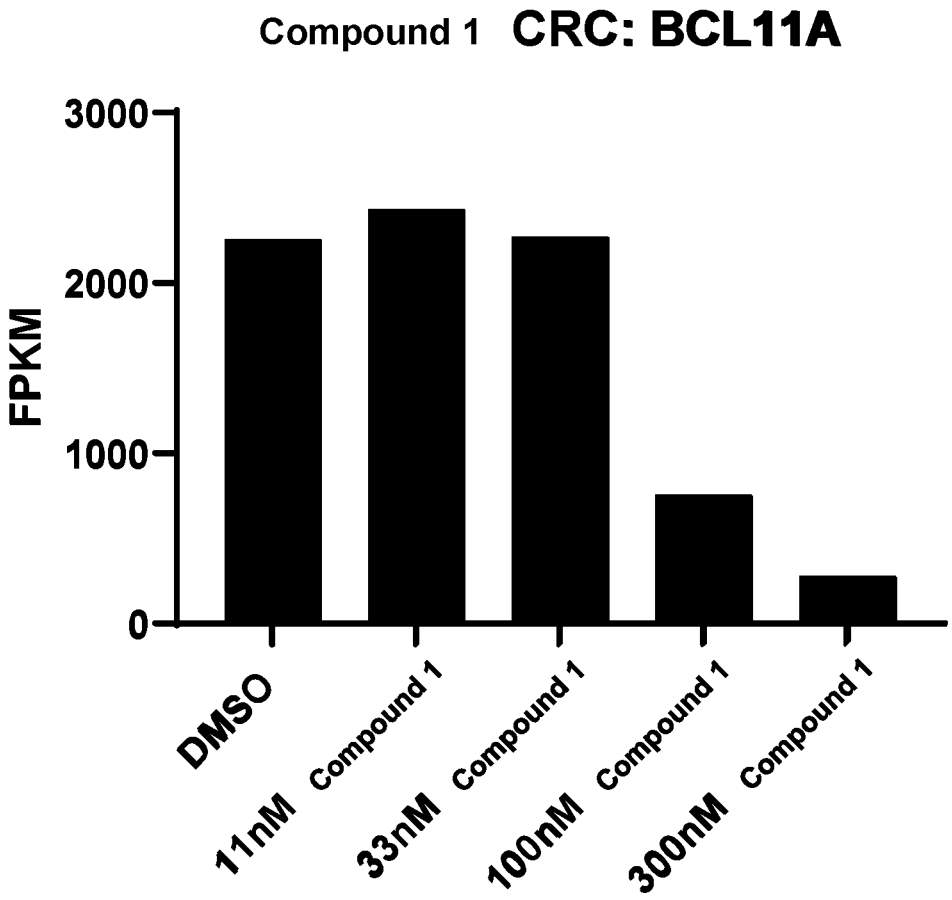

Compound 1 CRC: BCL11A
FPKM
3000
2000
1000
0
DMSO
11nM Compound 1
33nM Compound 1
100nM Compound 1
300nM Compound 1

FIG. 1

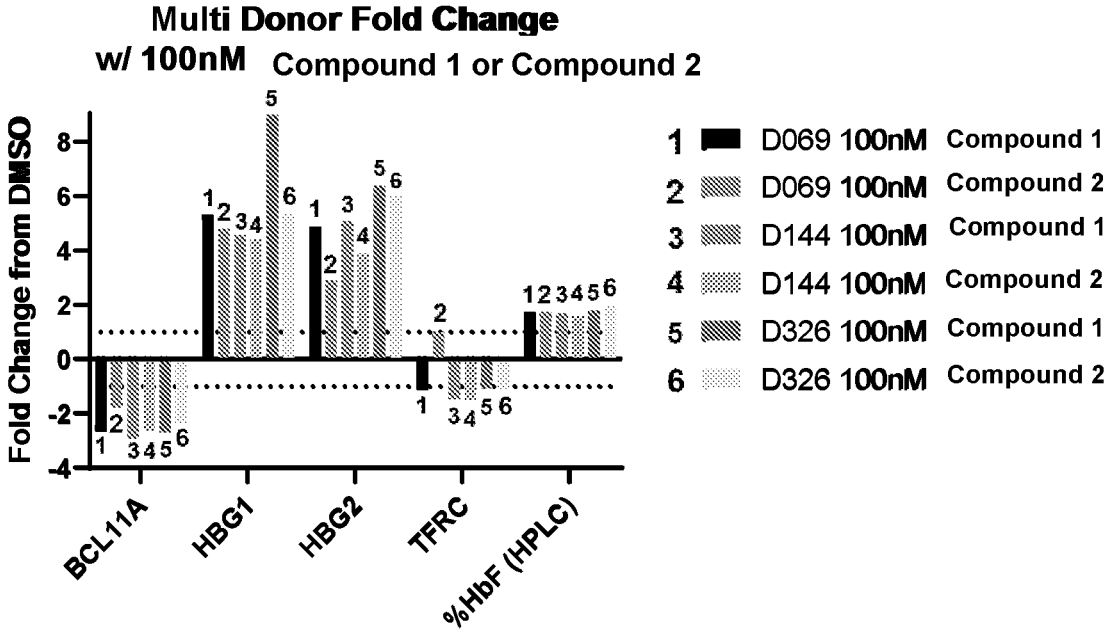

Multi Donor Fold Change
w/ 100nM Compound 1 or Compound 2
Fold Change from DMSO
8
6
4
2
0
-2
-4
BCL11A
HBG1
HBG2
TFRC
%HbF (HPLC)
1 D069 100nM Compound 1
2 D069 100nM Compound 2
3 D144 100nM Compound 1
4 D144 100nM Compound 2
5 D326 100nM Compound 1
6 D326 100nM Compound 2

FIG. 2

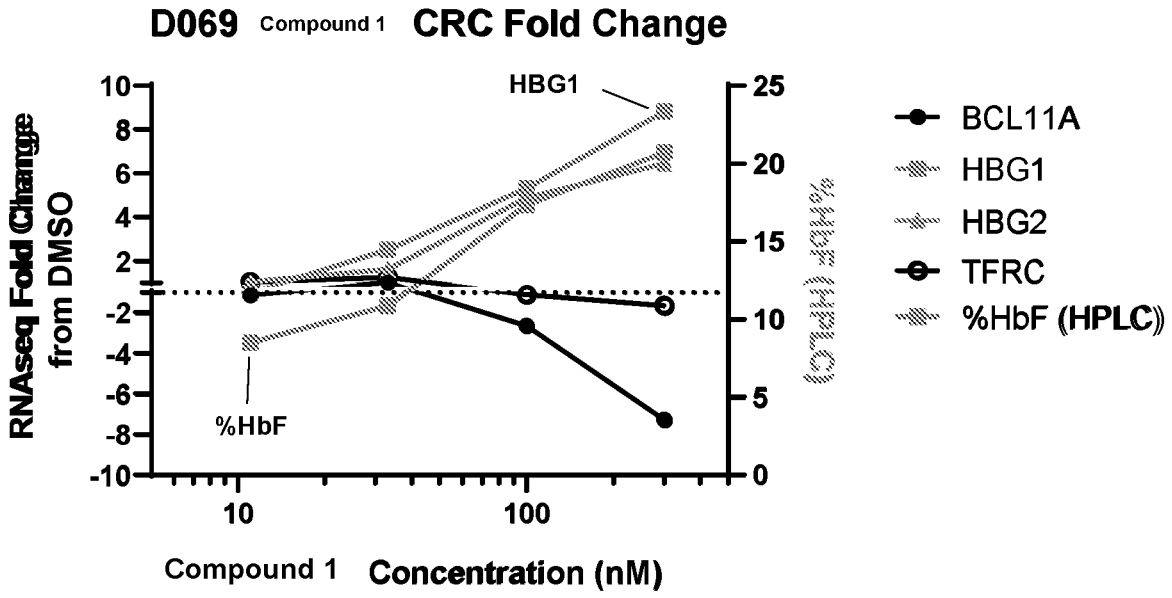

D069 Compound 1 CRC Fold Change
RNAseq Fold Change from DMSO
(total) %HbF
HBG1
%HbF
10
8
6
4
2
-2
-4
-6
-8
-10
25
20
15
10
5
0
10
100
Compound 1 Concentration (nM)
BCL11A
HBG1
HBG2
TFRC
%HbF (HPLC)

FIG. 3

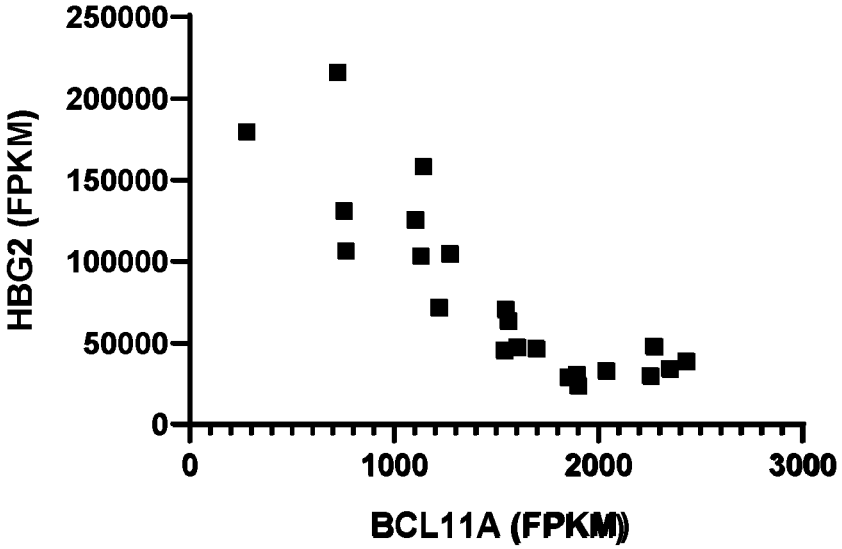

250000
200000
150000
100000
50000
0
HBG2 (FPKM)
0
1000
2000
3000
BCL11A (FPKM)

FIG. 4A

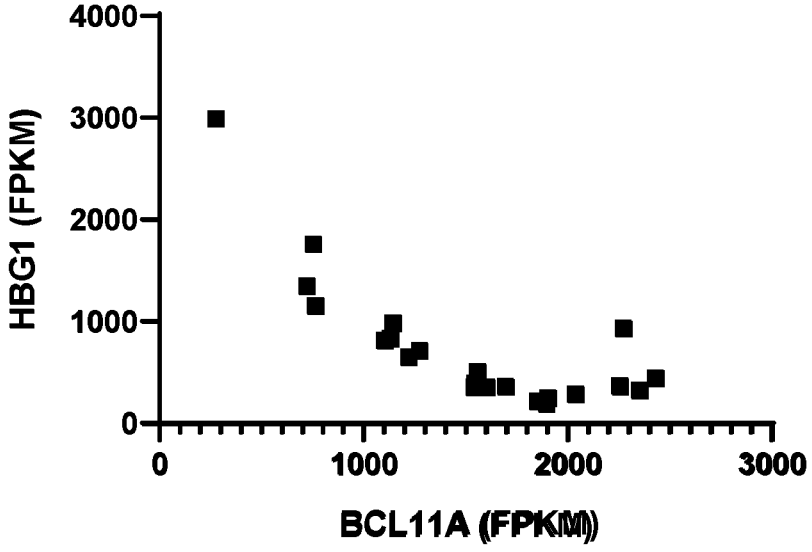

4000
3000
2000
1000
0
HBG1 (FPKM)
0
1000
2000
3000
BCL11A (FPKM)

FIG. 4B

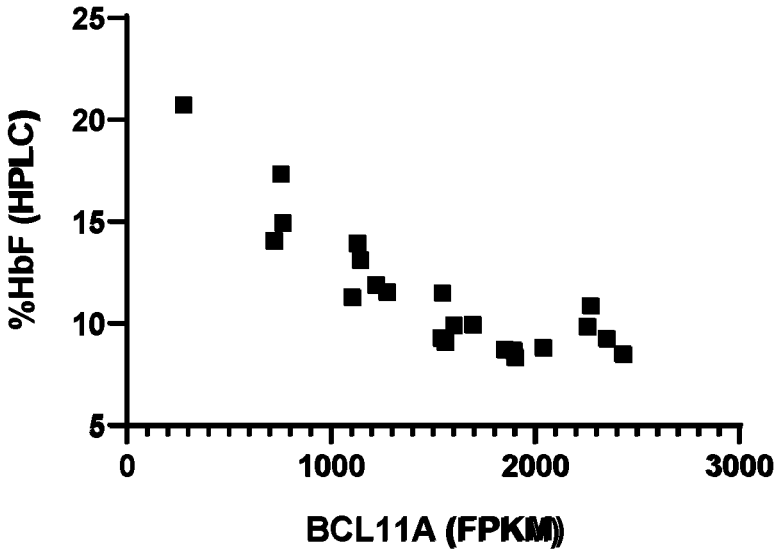



FIG. 4C

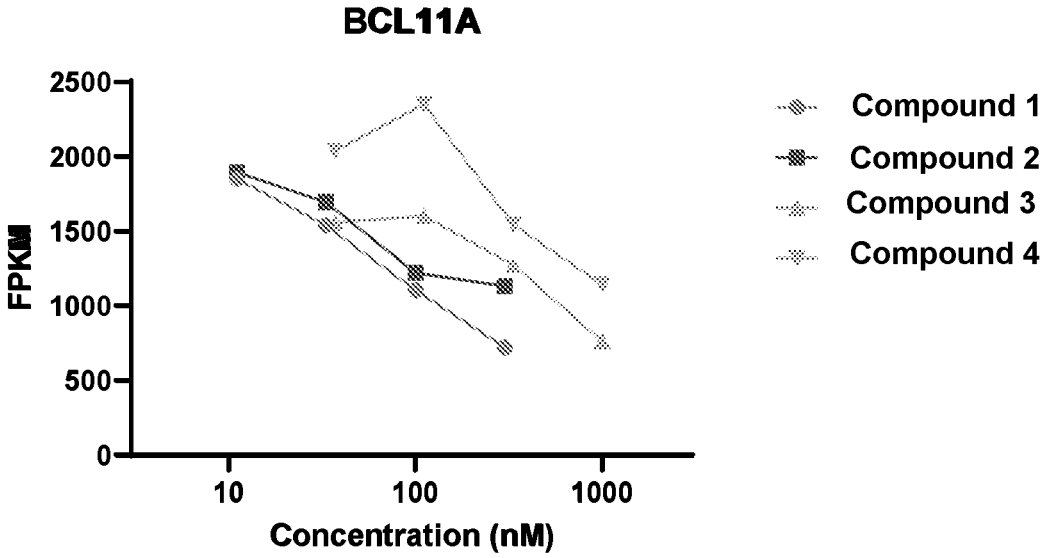

BCL11A
2500
2000
1500
1000
500
0
FPKM
10
100
1000
Concentration (nM)
Compound 1
Compound 2
Compound 3
Compound 4

FIG. 5A

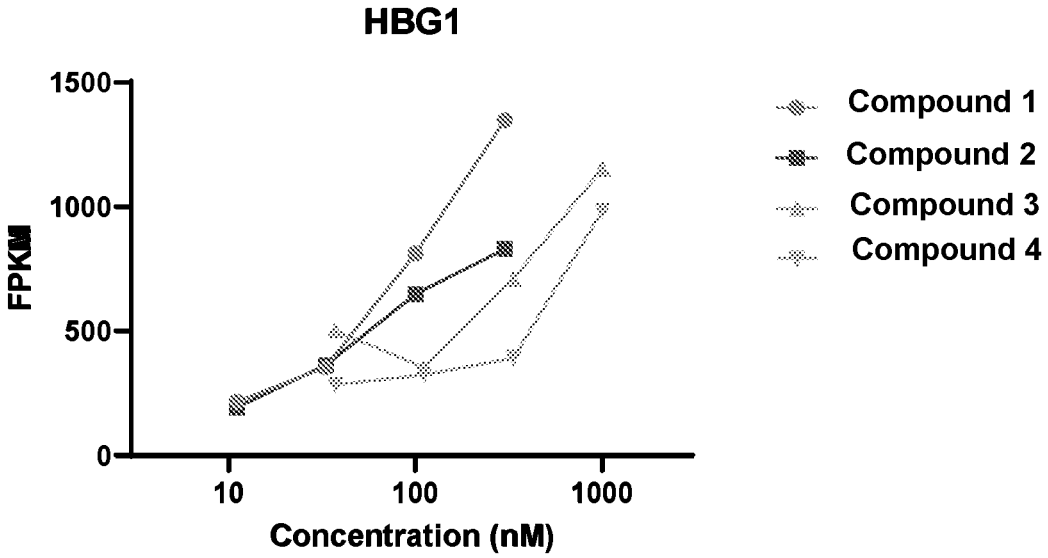

HBG1
1500
1000
500
0
FPKM
10
100
1000
Concentration (nM)
Compound 1
Compound 2
Compound 3
Compound 4

FIG. 5B

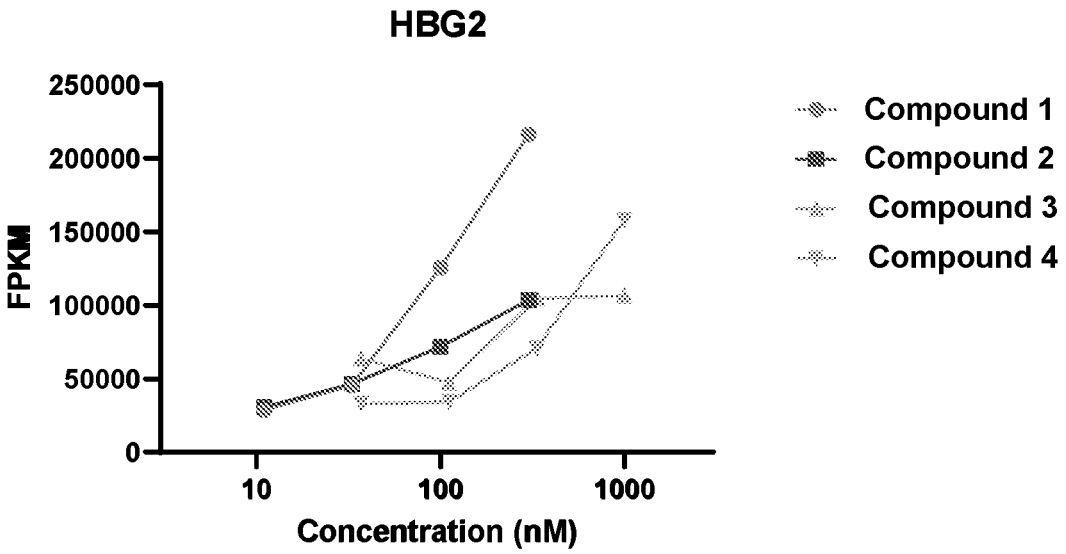

HBG2
250000
200000
150000
100000
50000
0
FPKM
10
100
1000
Concentration (nM)
Compound 1
Compound 2
Compound 3
Compound 4

FIG. 5C

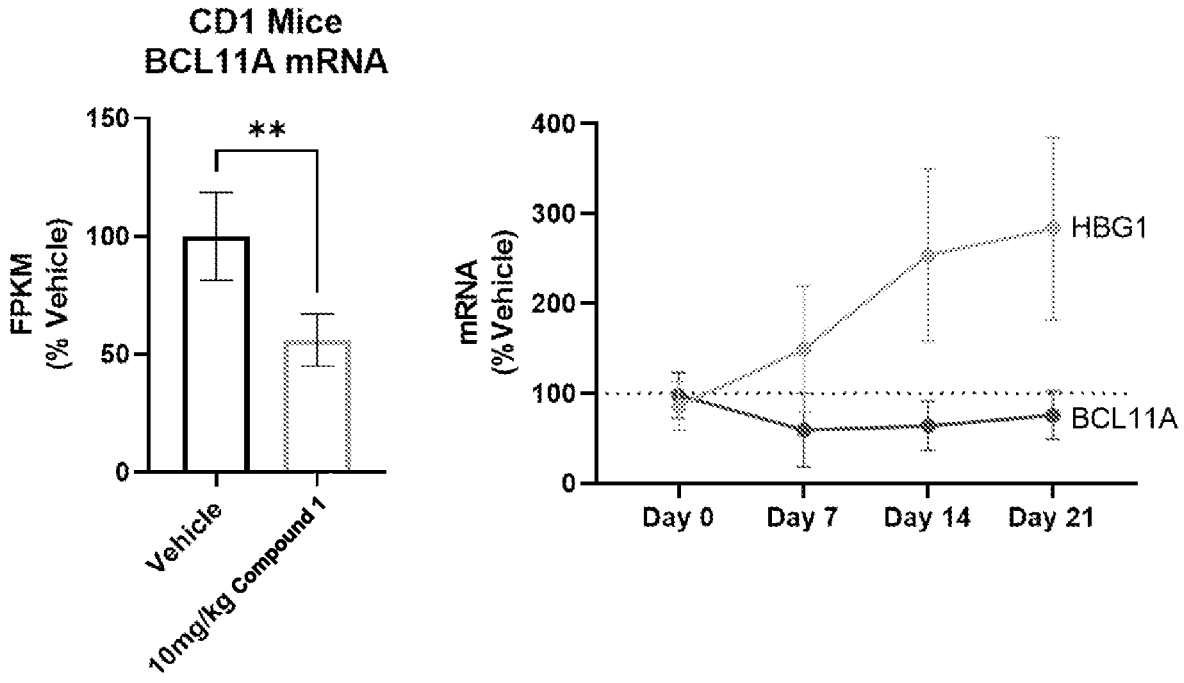

CD1 Mice
BCL11A mRNA
FPKM
(% Vehicle)
150
100
50
0
**
Vehicle
10mg/kg Compound 1
mRNA
(% Vehicle)
400
300
200
100
0
HBG1
BCL11A
Day 0
Day 7
Day 14
Day 21

FIG. 6

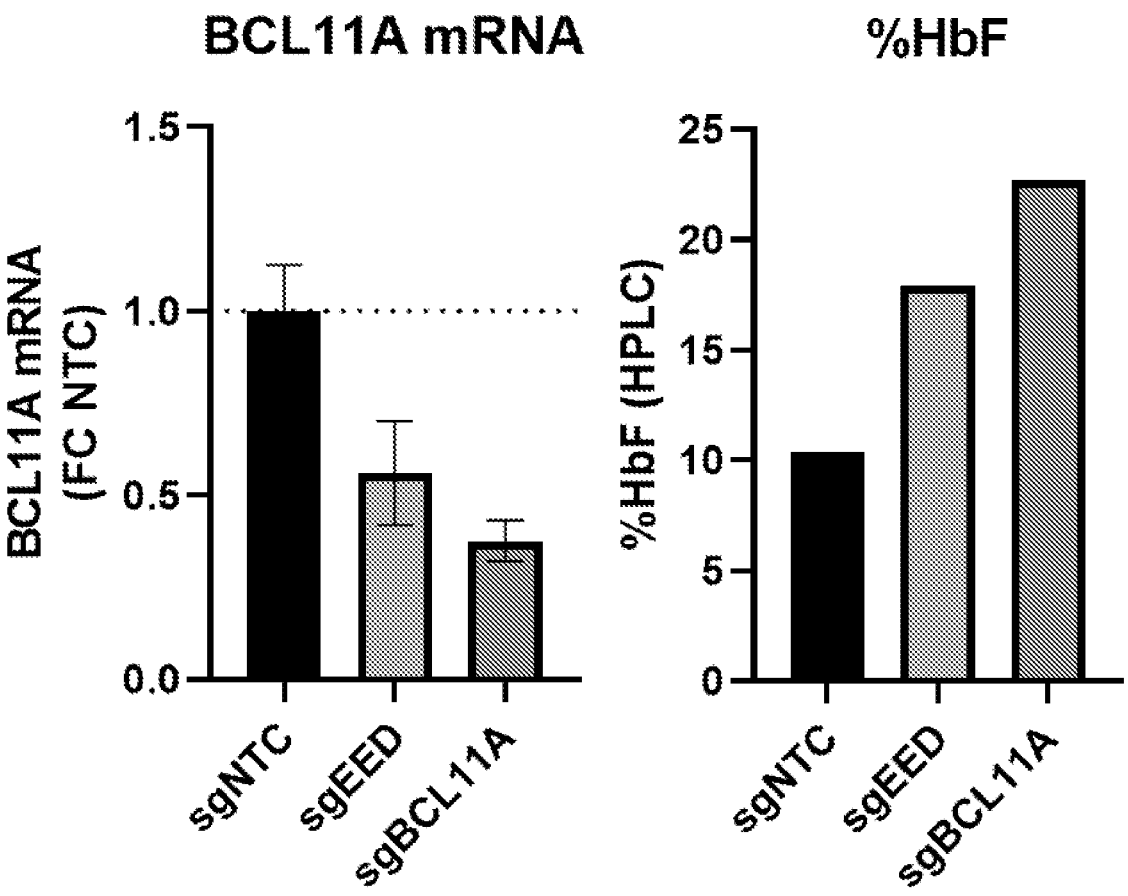

BCL11A mRNA
BCL11A mRNA (FC NTC)
1.5
1.0
0.5
0.0
sgNTC
sgEED
sgBCL11A
%HbF
%HbF (HPLC)
25
20
15
10
5
0
sgNTC
sgEED
sgBCL11A

FIG. 7

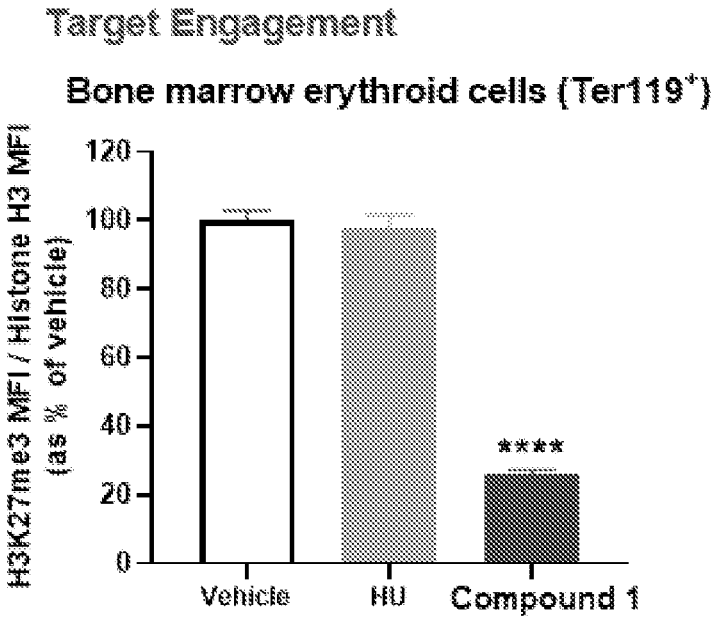

Target Engagement
Bone marrow erythroid cells (Ter119+)
H3K27me3 MFI / Histone H3 MFI (as % of vehicle)
120
100
80
60
40
20
0
****
Vehicle
HU
Compound 1

FIG. 8A

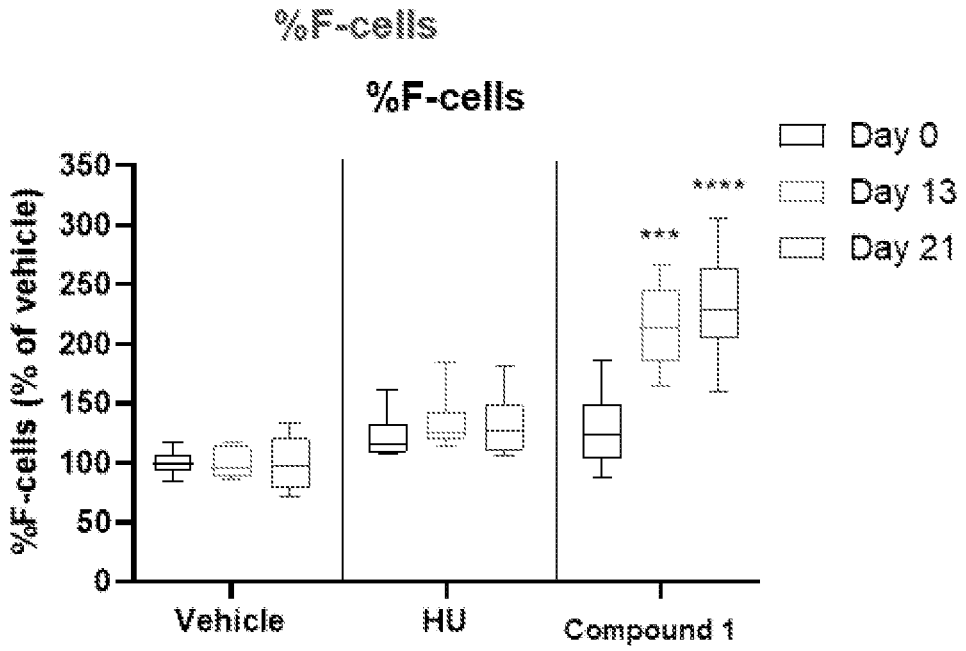

%F-cells
%F-cells
%F-cells (% of vehicle)
350
300
250
200
150
100
50
0
***
****
Day 0
Day 13
Day 21
Vehicle
HU
Compound 1

FIG. 8B

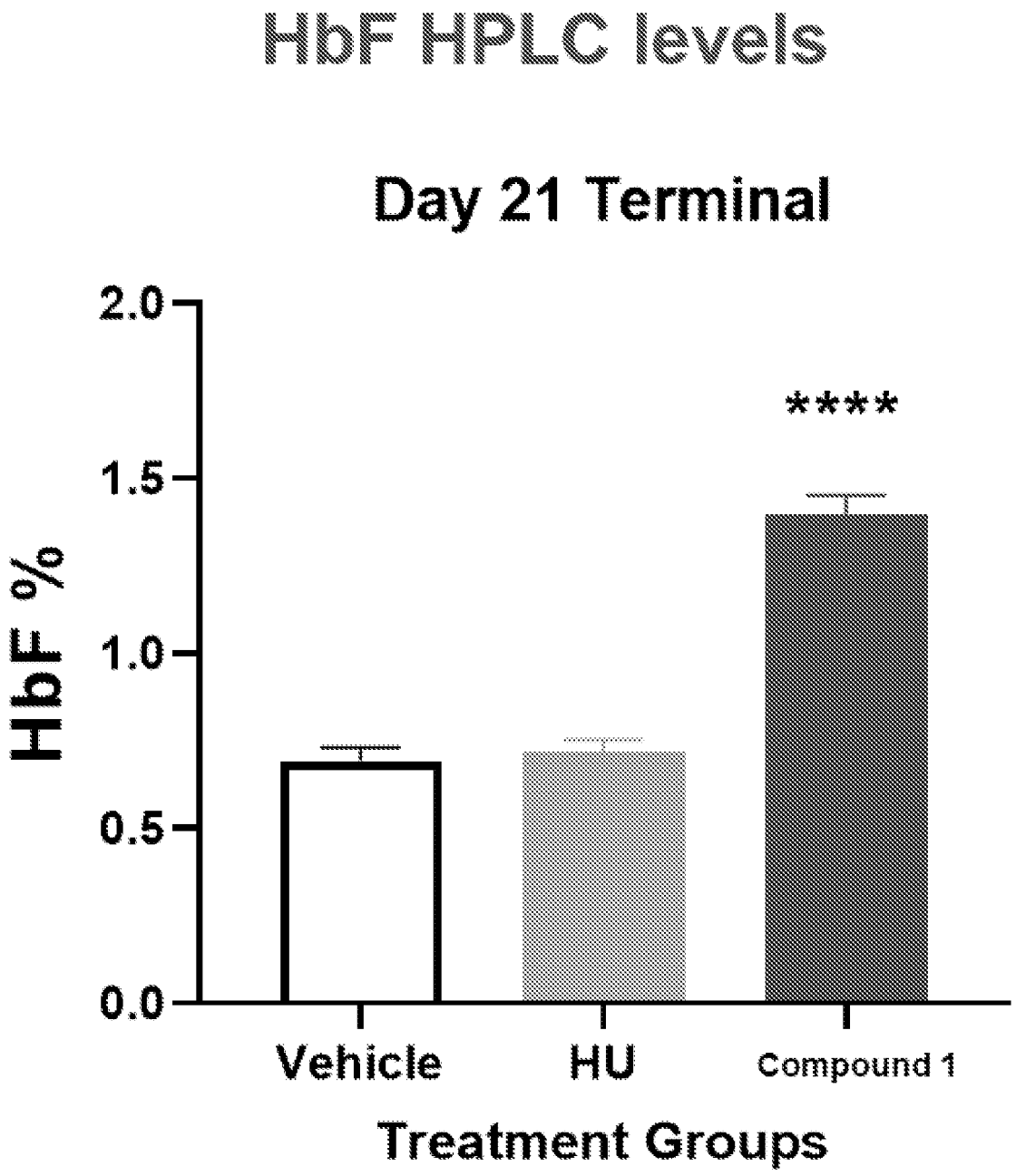

HbF HPLC levels
Day 21 Terminal
HbF %
2.0
1.5
1.0
0.5
0.0
****
Vehicle
HU
Compound 1
Treatment Groups

FIG. 8C

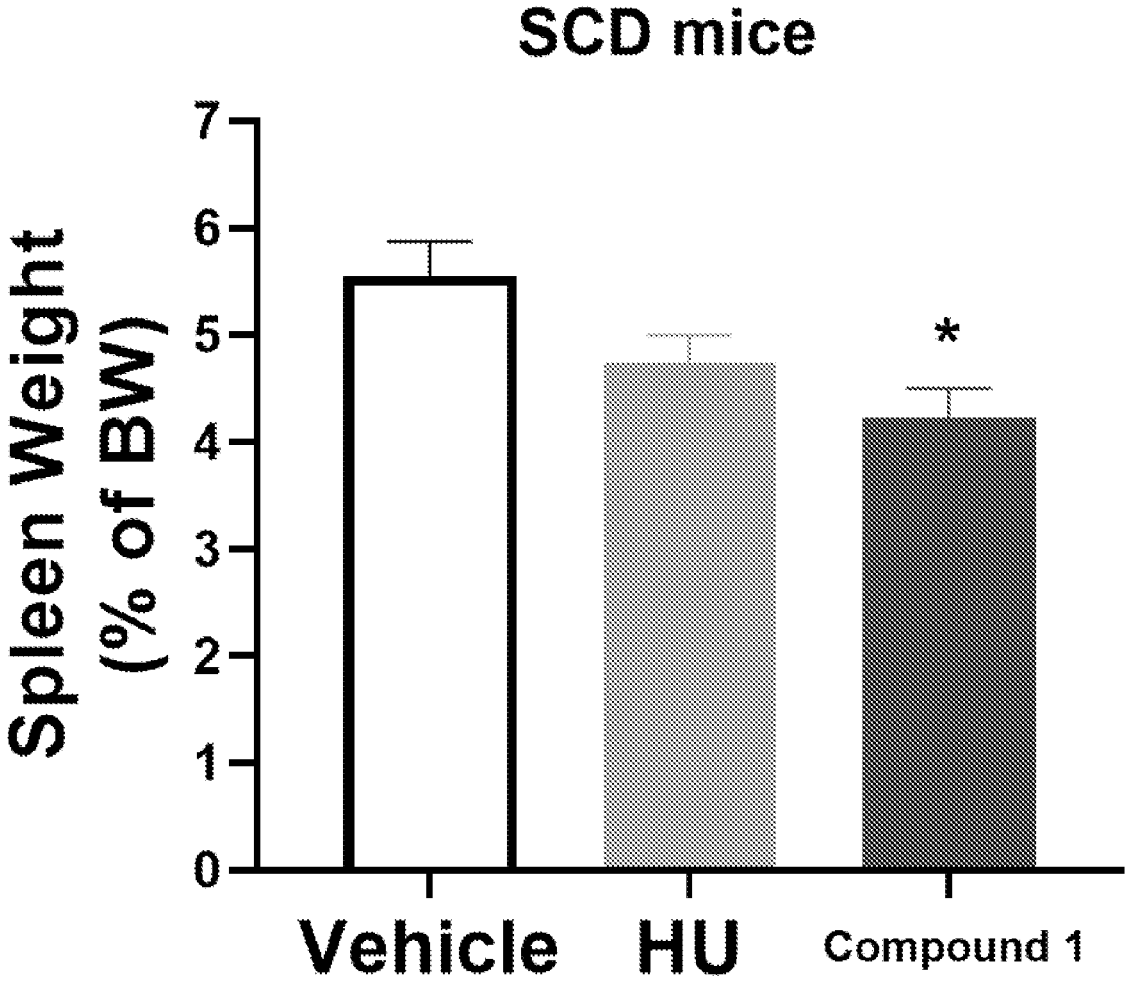



FIG. 8D

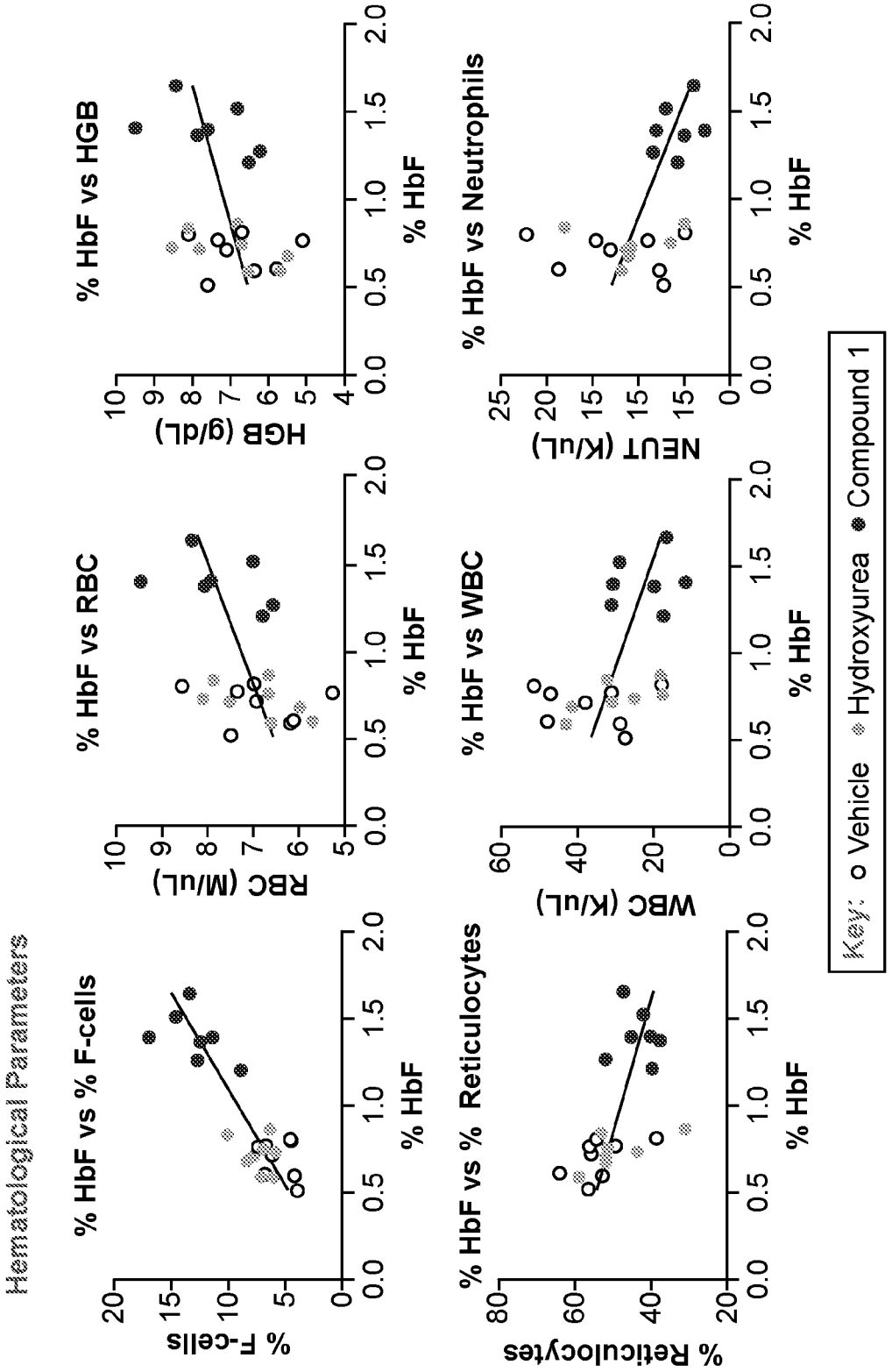

Hematological Parameters
% HbF vs % F-cells
% F-cells
% HbF
% HbF vs RBC
RBC (M/uL)
% HbF
% HbF vs HGB
HGB (g/dL)
% HbF
% HbF vs % Reticulocytes
% Reticulocytes
% HbF
% HbF vs WBC
WBC (K/uL)
% HbF
% HbF vs Neutrophils
NEUT (K/uL)
% HbF
Key: Vehicle Hydroxyurea Compound 1

FIG. 8E

# METHODS OF REGULATING BCL11A EXPRESSION AND TREATMENT OF BCL11A-MEDIATED DISORDERS

## CROSS-REFERENCE

**[0001]** This application claims priority to U.S. Provisional Application No. 63/181,747 filed Apr. 29, 2021, and U.S. Provisional Application No. 63/313,968 filed Feb. 25, 2022, the contents of each of which are incorporated herein by reference in their entireties.

## BACKGROUND

**[0002]** Polycomb group (PcG) proteins are a family of chromatin modifying enzymes that play a key role in gene expression and are dysregulated in many human diseases. The PcG family includes two classes of Polycomb Repressive Complexes (PRCs), namely Polycomb Repressive Complex 1 (PRC1) and Polycomb Repressive Complex 2 (PRC2). PRC2 includes SUZ12 (suppressor of zeste 12), EED (embryonic ectoderm development) and the catalytic subunit, EZH2 (enhancer of zeste homolog 2), and represses genes by methylating histone H3 lysine 27 (H3K27me3) at and around the promoter regions of genes. This critical component of chromatin regulation is involved in modulation of gene transcription and plays crucial function in development, differentiation, and regeneration. Although EZH2 is the catalytic subunit, PRC2 minimally requires EED and SUZ12 for its methyltransferase activity. EED, SUZ12 and EZH2 have been found to be overexpressed in many cancers, which include but are not limited to hepatocellular carcinoma, breast cancer, prostate cancer, etc. Activating mutations in EZH2 have been found in FL (follicular lymphoma) and DLBCL (diffuse large B cell lymphoma) patients. EED normally mediates repression of gene activity by binding to di- and trimethylated lysine 27 of histone 3 where it allosterically activates EZH2 activity of PRC2. EED has also been reported to recruit PRC1 to H3K27me3 loci and to enhance PRC1 mediated H2A ubiquitin E3 ligase activity.

**[0003]** Taken together, EED is a critical regulator of PRC2 in the silencing of expression of genes and gene clusters involved in development including but not limited to fetal orthologues (i.e. gamma globin), Hox genes, X chromosome inactivation, etc. Thus, EED provides a pharmacologic target for the treatment of diseases or disorders to impact transcription of specific target genes in blood and other tissues.

**[0004]** A need exists for small molecules that modulate EED, EHZ2, and/or PRC2.

## SUMMARY

**[0005]** Provided herein, in part, are methods of downregulating BCL11A expression and treatment of BCL11A mediated disorders.

**[0006]** Described herein, in one embodiment, is a method of downregulating BCL11A in a cell comprising: contacting the cell sample with an EED, EHZ2, and/or PRC2 inhibitor in amount sufficient to decrease expression of BCL11A.

**[0007]** In another embodiment, provided herein is a method of identifying a patient having a BCL11A mediated disorder who may benefit from treatment comprising one or more inhibitors of EED, EHZ2, and/or PRC2, comprising determining an expression level of BCL11A in a sample obtained from the patient, wherein an increased expression level of BCL11A in the sample as compared to a reference expression level identifies the patient as one who may benefit from the EED, EHZ2, and/or PRC2 inhibitor treatment.

**[0008]** In another embodiment, provided herein is a method of treating a patient having a BCL11A mediated disorder, comprising administering to the patient a therapeutically effective amount of a EED, EHZ2, and/or PRC2 inhibitor, wherein the expression level of BCL11A in a sample obtained from the patient has been determined to be decreased after the administration as compared to a reference expression level.

**[0009]** In another embodiment, provided herein is a method of treatment of a hemoglobinopathy in a subject comprising administering an effective amount of a composition comprising an inhibitor of EED, EHZ2, and/or PRC2, wherein the inhibitor of EED, EHZ2, and/or PRC2 downregulates the expression of BCL11A and whereby fetal hemoglobin expression is increased in the subject relative to prior to the administration.

**[0010]** In another embodiment, provided herein is a genetically modified cell comprising an insertion and/or deletion in a gene loci that encodes a protein selected from the group consisting of EED, EHZ2, and PRC2, wherein the insertion and/or deletion is capable of downregulating expression of BCL11A in the cell.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0011]** FIG. **1** depicts changes in the mRNA expression levels of BCL11A upon treatment with Compound 1 at various concentrations.

**[0012]** FIG. **2** depicts fold changes in BCL11A, HBG1, and HBG2 expression in exemplary CD34+ donor cells upon treatment with 100 nM Compound 1 or 100 nM Compound 2.

**[0013]** FIG. **3** depicts 4-point concentration response curves of fold changes in BCL11A expression, HBG1 expression, and HBG2 expression, and percentage HbF levels, in a CD34+ donor cell (D069) upon treatment with Compound 1 at various concentrations.

**[0014]** FIG. **4**A, FIG. **4**B, and FIG. **4**C depict aggregate data on the effect of HBG1 mRNA expression level (FIG. **4**A), HBG2 mRNA expression level (FIG. **4**B), and percentage HbF protein (FIG. **4**C) from two different CD34+ donors upon treatment with multiple compounds (Compound 1, Compound 2, Compound 3, and Compound 4 as described herein) that inhibit PRC2.

**[0015]** FIG. **5**A, FIG. **5**B, and FIG. **5**C depict 4-point concentration response curves of the effect of PRC2 inhibitors Compound 1, Compound 2, Compound 3, and Compound 4 on BCL11A expression (FIG. **5**A), HBG1 expression (FIG. **5**B), and HBG2 expression (FIG. **5**C).

**[0016]** FIG. **6** depicts BCL11A mRNA transcript levels by qRT-PCR in wild-type CD-1 mice and in the Townes sickle cell disease (SCD) mouse model upon treatment with Compound 1.

**[0017]** FIG. **7** depicts BCL11A mRNA transcript levels by qRT-PCR in CD34+ cells with CRISPR knockout of EED and BCL11A with corresponding HbF levels by HPLC.

**[0018]** FIG. **8**A depicts flow cytometry results of H3K27me3 for Compound 1 or hydroxyurea (HU) in bone marrow erythroid progenitors. FIG. **8**B depicts flow cytometry results of percent F-cell in terms of percentage of

vehicle for Compound 1 or HU. FIG. **8**C depicts HbF HPLC from whole blood after 21 days of treatment in studies with Compound 1 or HU. FIG. **8**D depicts results of Compound 1 or HU for mouse spleen weight percentage of total body weight. FIG. **8**E depicts percent HbF correlations to representative hematological parameters of anemia and inflammation in studies with Compound 1 or HU.

## DETAILED DESCRIPTION

**[0019]** Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications and this disclosure.

### Definitions

**[0020]** The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-5, 1-4, 1-3, or 1-2 carbon atoms, referred to herein as $C_1$-$C_6$ alkyl, $C_1$-$C_5$ alkyl, $C_1$-$C_4$ alkyl, $C_1$-$C_3$ alkyl, and $C_1$-$C_2$ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

**[0021]** The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as $C_2$-$C_6$ alkenyl, and $C_3$-$C_4$ alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

**[0022]** The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O—). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as $C_1$-$C_6$alkoxy, and $C_2$-$C_6$alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

**[0023]** The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6, or 3-6 carbon atoms, referred to herein as $C_2$-$C_6$alkynyl, and $C_3$-$C_6$alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

**[0024]** Unless otherwise specifically defined, the term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl). The aryl group may be optionally substituted by one or more substituents, e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, —H, —halogen, —O—$C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, —O$C_2$-$C_6$ alkenyl, —O$C_2$-$C_6$ alkynyl, —$C_2$-$C_6$ alkenyl, —$C_2$-$C_6$ alkynyl, —OH, —OP(O)$(OH)_2$, —OC(O)$C_1$-$C_6$ alkyl, —C(O)$C_1$-$C_6$ alkyl, —OC(O)O$C_1$-$C_6$ alkyl, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)$_2$, —S(O)$_2$-$C_1$-$C_6$ alkyl, —S(O)NH$C_1$-$C_6$ alkyl, and S(O)N($C_1$-$C_6$ alkyl)$_2$. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

**[0025]** The terms "cycloalkyl" or a "carbocyclic group" as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as $C_3$-$C_6$cycloalkyl or $C_4$-$C_6$cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

**[0026]** The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

**[0027]** The term "heteroaryl" as used herein refers to a monocyclic aromatic 5 or 6 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, said heteroaryl ring may be linked to the adjacent radical though carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, thiazole, oxazole, isothiazole, isoxazole, imidazole, pyrazole, triazole, pyridine or pyrimidine etc.

**[0028]** The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated, 4-10 membered ring structures, including monocyclic, bridged or fused rings, and whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc.

**[0029]** "Spirocycloalkyl" or "spirocyclyl" means carbogenic bicyclic ring systems with both rings connected through a single atom. The ring can be different in size and nature, or identical in size and nature. Examples include spiropentane, spriohexane, spiroheptane, spirooctane, spirononane, or spirodecane. One or both of the rings in a spirocycle can be fused to another carbocyclic, heterocyclic, aromatic, or heteroaromatic ring. One or more of the carbon atoms in the spirocycle can be substituted with a heteroatom (e.g., O, N, S, or P). A ($C_5$-$C_{12}$) spirocycloalkyl is a spirocycle containing between 5 and 12 carbon atoms. One or more of the carbon atoms can be substituted with a heteroatom.

**[0030]** The term "spiroheterocycloalkyl" or "spiroheterocyclyl" is understood to mean a spirocycle wherein at least one of the atoms in one of the rings is a heteroatom. In some embodiments, at least one of the atoms in one of the rings is O, N, S, or P.

**[0031]** The term "oxo" as used herein refers to an "=O" group.

**[0032]** "Individual," "patient," or "subject" are used interchangeably herein and include any animal, including mam-

mals, including mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and humans. The compounds described herein can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). The mammal treated in the methods described herein is desirably a mammal in which treatment of a disorder described herein is desired, such as a human.

**[0033]** As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

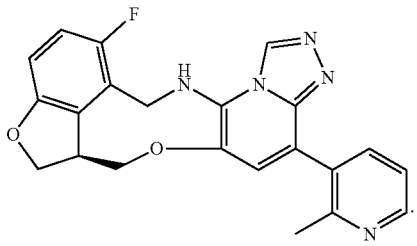
**[0034]** Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{14}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

**[0035]** Unless otherwise stated, structures depicted herein are also meant to include all enantiomeric, diastereomeric, and geometric (or conformational) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the present disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the present disclosure are within the scope of the present disclosure.

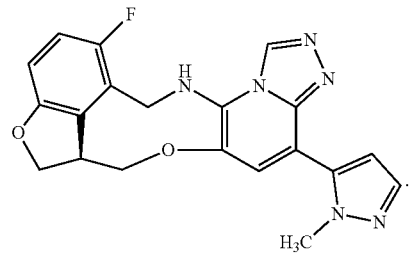
**[0036]** "Therapeutically effective amount" includes the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. A compound described herein, e.g., an EED, EHZ2, and/or PRC2 inhibitor, is administered in therapeutically effective amounts to treat a condition, e.g., a condition described herein. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with the condition.

**[0037]** A compound described herein, e.g., an EED, EHZ2, and/or PRC2 inhibitor, can be formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and administered by a variety of routes. In some embodiments, such compositions are for oral administration. In some embodiments, such compositions are for parenteral (by injection) administration. In some embodiments, such compositions are for transdermal administration. In some embodiments, such compositions are for intravenous (IV) administration. In some embodiments, such compositions are for intramuscular (IM) administration. Such pharmaceutical compositions and processes for preparing them are well known in the art. See, e.g., REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995). Dosages of compounds described herein in oral compositions include, but are not limited to, 6 mg.

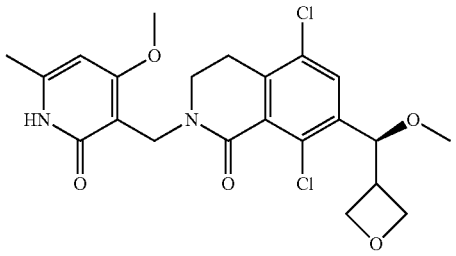
**[0038]** "Compound 1" as described herein, refers to a compound represented by:



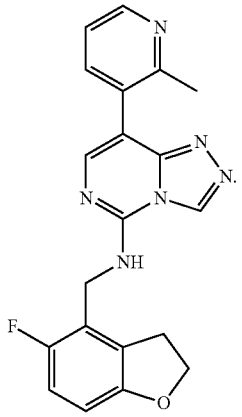
**[0039]** "Compound 2" as described herein, refers to a compound represented by:



**[0040]** "Compound 3" as described herein, refers to a compound represented by:



**[0041]** "Compound 4" as described herein, refers to a compound represented by:



Downregulation of BCL11A Expression

**[0042]** The present disclosure provides, in an embodiment, methods of downregulating expression of BCL11A.

**[0043]** A method of downregulating BCL11A described herein is, in an embodiment, a method of downregulating BCL11A in a cell comprising: contacting the cell sample with an EED, EHZ2, and/or PRC2 inhibitor in amount sufficient to decrease expression of BCL11A. In some embodiments, the cell is an erythroid cell differentiated from a CD34+ cell. In some embodiments, upon contacting the cell, HBG1 and/or HBG2 expression increases. In some embodiments, upon contacting the cell with the protein inhibitor, the cell does or does not express fetal hemoglobin. In some embodiments, the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of an antibody against EED, EHZ2, and/or PRC2 or an antigen-binding fragment thereof, a small molecule, and a nucleic acid. In some embodiments, the nucleic acid is a EED, EHZ2, and/or PRC2-specific RNA interference agent, a vector encoding a RNA interference agent, or an aptamer that binds EED, EZH2, and/or PRC2. In some embodiments, the expression level of BCL11A is decreased by at least 25% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 50% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 75% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 90% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 99% relative to a reference level. In some embodiments, the expression level is a protein expression level or a mRNA expression level. In some embodiments, the mRNA expression level is determined by qPCR or RNA-Seq. In some embodiments, the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

Methods of Treatment

**[0044]** The present disclosure also provides, in another embodiment, methods of treating BCL11A mediated disorders in a patient in need thereof, comprising administering to the patient a therapeutic agent described herein, e.g., an EED, EHZ2, and/or PRC2 inhibitor. Exemplary BCL11A mediated disorders include, but are not limited to, triple negative breast cancer, non-small cell lung cancer, glioblastoma, neuroblastoma, prostate cancer, type 2 diabetes, laryngeal squamous cell carcinoma, and Williams syndrome.

**[0045]** Described herein, in another embodiment, is a method of identifying a patient having a BCL11A mediated disorder who may benefit from treatment comprising one or more inhibitors of EED, EHZ2, and/or PRC2, comprising determining an expression level of BCL11A in a sample obtained from the patient, wherein an increased expression level of BCL11A in the sample as compared to a reference expression level identifies the patient as one who may benefit from the EED, EHZ2, and/or PRC2 inhibitor treatment. In some embodiments, the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of an antibody against EED, EHZ2, and/or PRC2 or an antigen-binding fragment thereof, a small molecule, and a nucleic acid. In some embodiments, the nucleic acid is a EED, EHZ2, and/or PRC2-specific RNA interference agent, a vector encoding a RNA interference agent, or an aptamer that binds EED, EZH2, and/or PRC2. In some embodiments, the BCL11A mediated disorder is selected from the group consisting of triple negative breast cancer, non-small cell lung cancer, glioblastoma, neuroblastoma, prostate cancer, type 2 diabetes, laryngeal squamous cell carcinoma, and Williams syndrome. In some embodiments, the expression level of BCL11A is decreased by at least 25% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 50% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 75% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 90% relative to a reference

level. In some embodiments, the expression level of BCL11A is decreased by at least 99% relative to a reference level. In some embodiments, the expression level is a protein expression level or a mRNA expression level. In some embodiments, the mRNA expression level is determined by qPCR or RNA-Seq. In some embodiments, the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

**[0046]** Also described herein, in another embodiment, is a method of treating a patient having a BCL11A mediated disorder, comprising administering to the patient a therapeutically effective amount of a EED, EHZ2, and/or PRC2 inhibitor, wherein the expression level of BCL11A in a sample obtained from the patient has been determined to be decreased after the administration as compared to a reference expression level. In some embodiments, the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of an antibody against EED, EHZ2, and/or PRC2 or an antigen-binding fragment thereof, a small molecule, and a nucleic acid. In some embodiments, the nucleic acid is a EED, EHZ2, and/or PRC2-specific RNA interference agent, a vector encoding a RNA interference agent, or an aptamer that binds EED, EZH2, and/or PRC2. In some embodiments, the BCL11A mediated disorder is selected from the group consisting of triple negative breast cancer, non-small cell lung cancer, glioblastoma, neuroblastoma, prostate cancer, type 2 diabetes, laryngeal squamous cell carcinoma, and Williams syndrome. In some embodiments, the expression level of BCL11A is decreased by at least 25% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 50% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 75% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 90% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 99% relative to a reference level. In some embodiments, the expression level is a protein expression level or a mRNA expression level. In some embodiments, the mRNA expression level is determined by qPCR or RNA-Seq. In some embodiments, the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

**[0047]** Further described herein, in another embodiment, is a method of treatment of a hemoglobinopathy in a subject comprising administering an effective amount of a composition comprising an inhibitor of EED, EHZ2, and/or PRC2, wherein the inhibitor of EED, EHZ2, and/or PRC2 downregulates the expression of BCL11A and whereby fetal hemoglobin expression is increased in the subject relative to prior to the administration. In some embodiments, the hemoglobinopathy is selected from the group consisting of sickle cell disease (SCD), α-thalassemia, and β-thalassemia. In some embodiments, the β-thalassemia is selected from the group consisting of sickle β-thalassemia, hemoglobin C β-thalassemia, and hemoglobin E β-thalassemia. In some embodiments, the sickle β-thalassemia is selected from sickle BO thalassemia and sickle β+ thalassemia. In some embodiments, the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of an antibody against EED, EHZ2, and/or PRC2 or an antigen-binding fragment thereof, a small molecule, and a nucleic acid. In some embodiments, the nucleic acid is a EED, EHZ2, and/or PRC2-specific RNA interference agent, a vector encoding a RNA interference agent, or an aptamer that binds EED, EZH2, and/or PRC2. In some embodiments, the expression level of BCL11A is decreased by at least 25% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 50% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 75% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 90% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 99% relative to a reference level. In some embodiments, the expression level is a protein expression level or a mRNA expression level. In some embodiments, the mRNA expression level is determined by qPCR or RNA-Seq. In some embodiments, the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

## Genetically Modified Cells

**[0048]** The present disclosure additionally provides, in another embodiment, a genetically modified cell comprising an insertion and/or deletion in a gene loci that encodes a protein selected from the group consisting of EED, EHZ2, and PRC2, wherein the insertion and/or deletion is capable of downregulating expression of BCL11A in the cell. In some embodiments, the expression level of BCL11A is decreased by at least 25% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 50% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 75% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 90% relative to a reference level. In some embodiments, the expression level of BCL11A is decreased by at least 99% relative to a reference level. In some embodiments, the expression level is a protein expression level or a mRNA expression level. In some embodiments, the mRNA expression level is determined by qPCR or RNA-Seq. In some embodiments, the protein expression

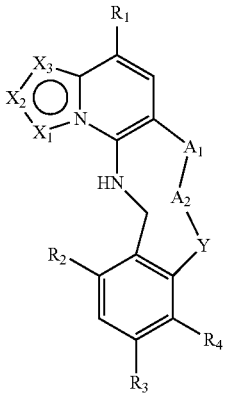
level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

## Inhibitors

**[0049]** The present disclosure also provides, in some embodiments, inhibitors useful in the methods described herein. Such inhibitors may include EED, EHZ2, and/or PRC2 inhibitors.

**[0050]** In one embodiment, an inhibitor described herein is represented by a compound of Formula I:

(I)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein:

**[0051]** $X_1$, $X_2$, and $X_3$ are independently N or $C(R_5)$, provided that $X_1$, $X_2$, and $X_3$ are not all N and at least one of $X_1$, $X_2$, or $X_3$ is N;

**[0052]** A1 is a bond, $C(R_8)(R_9)$—, —O—,—$NR_8$, —S—,—S(O)—, or —$SO_2$—;

**[0053]** A2 and Y are independently at each occurrence —$C(R_8)(R_9)$—, —O—, —$NR_8$, —S—, —S(O)—, or —$SO_2$—;

**[0054]** $R_1$ is H, halogen, —$NR_8R_9$, —$P(O)(OR_8)(OR_9)$, —$C(O)R_8$, —$C(O)NR_8R_9$, —CN, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_6$;

**[0055]** $R_2$ and $R_3$ are independently at each occurrence H, halogen, —OH, —$NH_2$, —CN, C1-C6 alkyl, C1-C6 alkoxy, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, wherein the alkyl, alkoxy, alkenyl, or alkynyl is optionally substituted with one or more $R_7$;

**[0056]** $R_4$ is H, halogen, —OH, —$NH_2$, —CN, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, wherein the alkyl, alkoxy, alkenyl, or alkynyl is optionally substituted with one or more $R_7$,

**[0057]** or $R_4$ and $R_9$ when taken together can form $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$;

**[0058]** $R_5$ is H, halogen, —CN, —$OR_8$, —$NR_8R_9$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_7$;

**[0059]** $R_6$ is independently at each occurrence oxo, halogen, —CN, OH, —$NR_8R_9$, —$OR_8$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$; or

**[0060]** two $R_6$ can combine to form $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$;

**[0061]** $R_7$ is independently at each occurrence oxo, halogen, —CN, —$OR_8$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl;

**[0062]** $R_8$ is independently at each occurrence H, OH, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$;

**[0063]** $R_9$ is independently at each occurrence H, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$;

**[0064]** or $R_8$ and $R_9$ when taken together form a $C_3$-$C_6$ cycloalkyl or heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with $R_{10}$; and

**[0065]** Ro is independently at each occurrence oxo, halogen, —CN, —$OR_{11}$, —$C(O)R_{11}$, —$C(O)OR_{11}$, —$C(O)NR_{11}R_{12}$, —$NR_{11}R_{12}$, —$NR_{11}C(O)R_{12}$, —$S(O)R_{11}$, —$S(O)_2R_{11}$, —$NR_{11}S(O)_2R_{12}$, —$S(O)_2NR_{11}R_{12}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

**[0066]** $R_{11}$ and $R_{12}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0067]** In some embodiments, $X_1$ is N or $C(R_5)$. In some embodiments, $X_1$ is N. In some embodiments, $X_1$ is $C(R_5)$. In some embodiments, $X_2$ is N. In some embodiments, $X_2$ is $C(R_5)$. In some embodiments, $X_3$ is N. In some embodiments, $X_3$ is $C(R_5)$.

**[0068]** In some embodiments, $A_1$ is a bond, —$C(R_8)(R_9)$—, —O—, —$NR_8$—, —S—, —S(O)—, or —$SO_2$—.

**[0069]** In some embodiments, $A_2$ and Y are independently at each occurrence —$C(R_8)(R_9)$—, —O—, —$NR_8$—, or —$SO_2$—.

**[0070]** In some embodiments, $A_1$ is —$C(R_8)(R_9)$—, —O—, —$NR_8$—, —S—, —S(O)—, or —$SO_2$—. In some embodiments, $A_1$ is a bond. In some embodiments, $A_1$ is

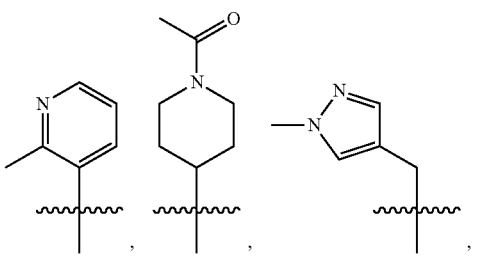
—$C(R_8)(R_9)$— or —O—. In some embodiments, $A_1$ is —$C(R_8)(R_9)$—. In some embodiments, $A_1$ is—O—. In some embodiments, $A_1$ is —$NR_8$—. In some embodiments, $A_1$ is —S—. In some embodiments, $A_1$ is —S(O)—. In some embodiments, $A_1$ is —$SO_2$—.

**[0071]** In some embodiments, $A_2$ is —$C(R_8)(R_9)$—, —O—, —$NR_8$—, or —$SO_2$—. In some embodiments, $A_2$ is —$C(R_8)(R_9)$— or —O—. In some embodiments, $A_2$ is —$C(R_8)(R_9)$—. In some embodiments, $A_2$ is —O—. In some embodiments, $A_2$ is —$NR_8$—. In some embodiments, $A_2$ is —S—. In some embodiments, $A_2$ is —S(O)—. In some embodiments, $A_2$ is —$SO_2$—.

**[0072]** In some embodiments, Y is —$C(R_8)(R_9)$—, —O—, —$NR_8$—, or —$SO_2$—. In some embodiments, Y is —$C(R_8)(R_9)$— or —O—. In some embodiments, Y is —$C(R_8)(R_9)$—. In some embodiments, Y is —O—. In some embodiments, Y is —$NR_8$—. In some embodiments, Y is —S—. In some embodiments, Y is —S(O)—. In some embodiments, Y is —$SO_2$—.

**[0073]** In some embodiments, $R_1$ is H, halogen, —$NR_8R_9$, —$P(O)(OR_8)(OR_9)$, —$C(O)R_8$, —$C(O)NR_8R_9$, —CN, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_1$ is H. In some embodiments, $R_1$ is —$NR_8R_9$. In some embodiments, $R_1$ is —$P(OR_8)(OR_9)$. In some embodiments, $R_1$ is —$C(O)R_8$. In some embodiments, $R_1$ is —$C(O)NR_8R_9$. In some embodiments, $R_1$ is —CN. In some embodiments, $R_1$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_1$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_1$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_1$ is $C_2$-$C_6$ alkynyl. In some embodiments, $R_1$ is $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_1$ is $C_3$-$C_8$ spirocycloalkyl. In some embodiments, $R_1$ is spiroheterocyclyl. In some embodiments, $R_1$ is heterocyclyl. In some embodiments, $R_1$ is aryl. In some embodiments, $R_1$ is heteroaryl.

**[0074]** In some embodiments, $R_1$ is $C_1$-$C_6$ alkyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is $C_1$-$C_6$ alkoxy is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is $C_2$-$C_6$ alkenyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is $C_2$-$C_6$ alkynyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is $C_3$-$C_{10}$ cycloalkyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is $C_3$-$C_8$ spirocycloalkyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is spiroheterocyclyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is heterocyclyl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is aryl is optionally substituted with one or more $R_6$. In some embodiments, $R_1$ is heteroaryl is optionally substituted with one or more $R_6$.



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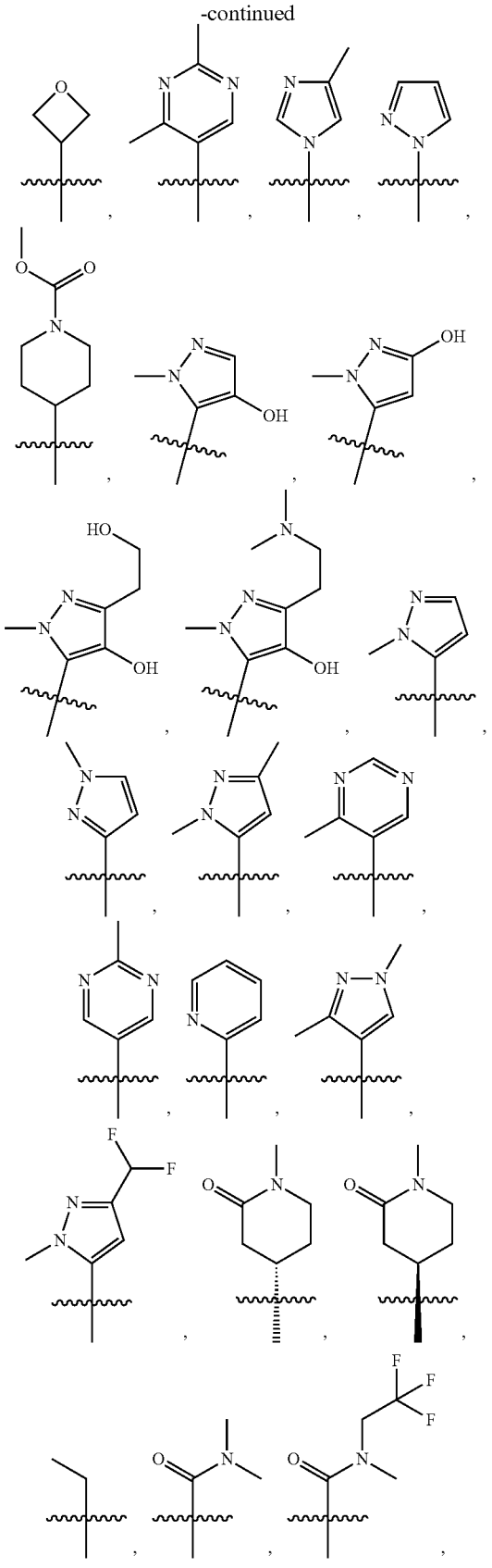

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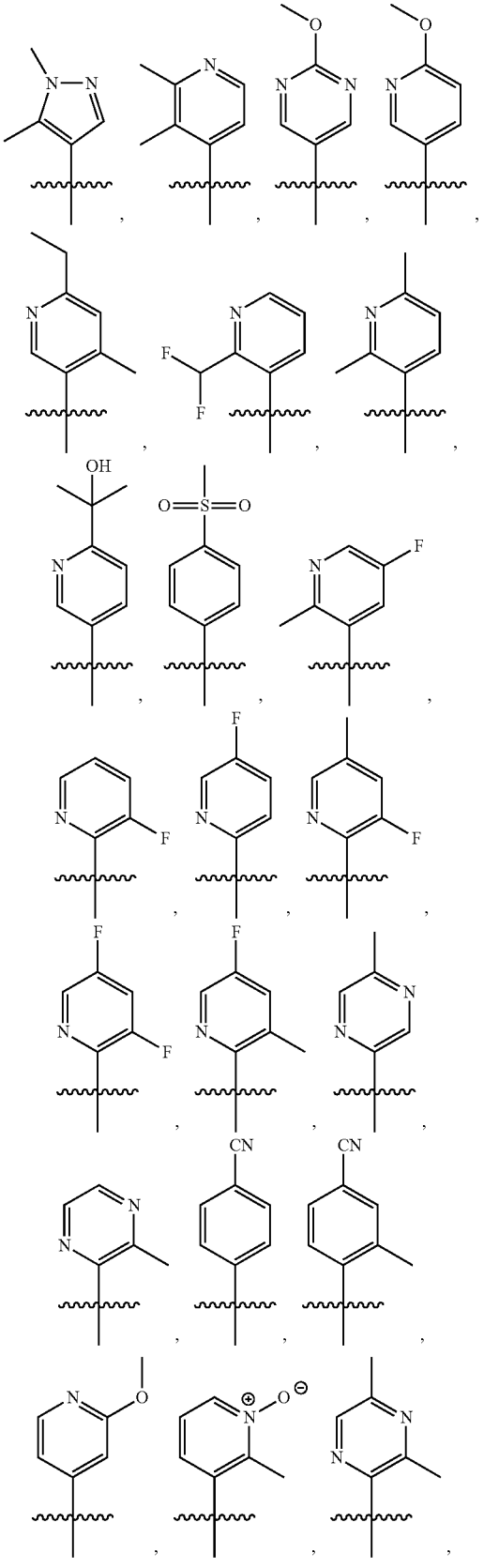

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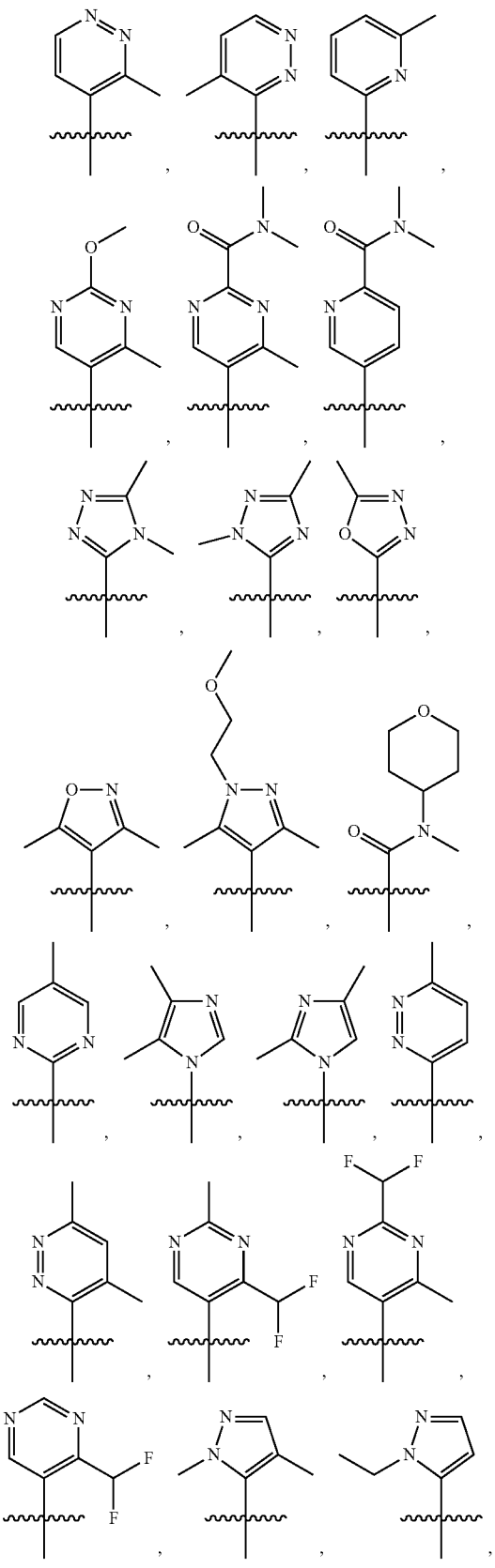

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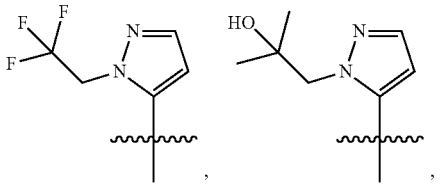
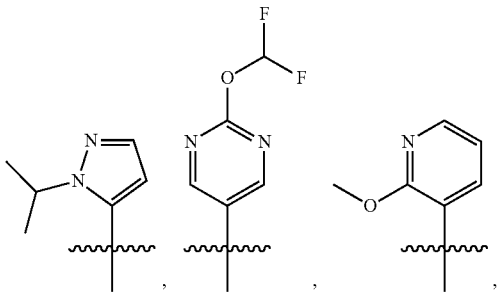
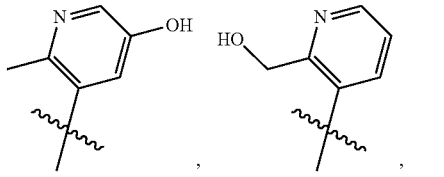
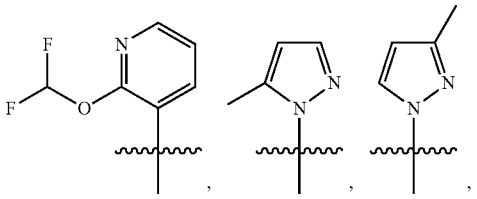
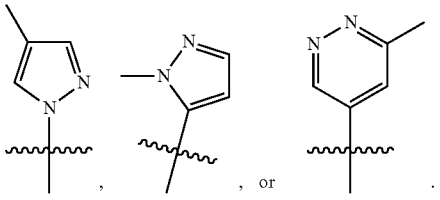


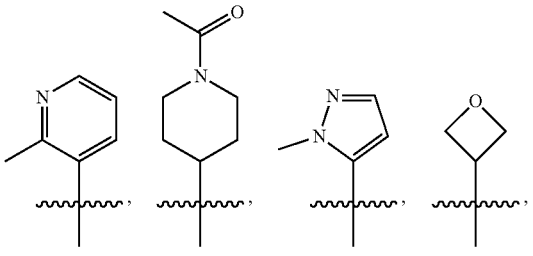








**[0075]** In another embodiment, $R_1$ is



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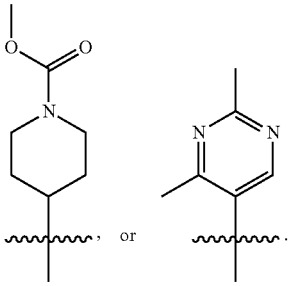
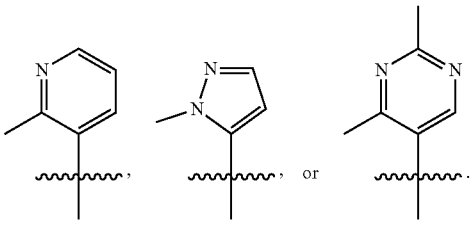
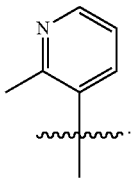


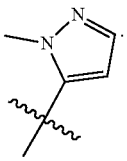
**[0076]** In another embodiment, $R_1$ is



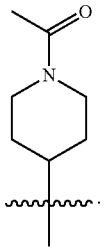
**[0077]** In another embodiment, $R_1$ is



**[0078]** In another embodiment, $R_1$ is



**[0079]** In another embodiment, $R_1$ is



**[0080]** In some embodiments, $R_1$ is

**[0081]** In some embodiments, $R_2$ is independently at each occurrence H, halogen, —OH, —$NH_2$, —CN, $C_1$-$C_6$ alkyl,

$C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl. In some embodiments, $R_2$ is H. In some embodiments, $R_2$ is halogen. In some embodiments, $R_2$ is —OH. In some embodiments, $R_2$ is —$NH_2$. In some embodiments, $R_2$ is —CN. In some embodiments, $R_2$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_2$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_2$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_2$ is $C_2$-$C_6$ alkynyl.

**[0082]** In some embodiments, $R_2$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_7$. In some embodiments, $R_2$ is $C_1$-$C_6$ alkoxy optionally substituted with one or more $R_7$. In some embodiments, $R_2$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_7$. In some embodiments, $R_2$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_7$.

**[0083]** In some embodiments, $R_3$ is independently at each occurrence H, halogen, —OH, —$NH_2$, —CN, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl. In some embodiments, $R_3$ is H. In some embodiments, $R_3$ is halogen. In some embodiments, $R_3$ is —OH. In some embodiments, $R_3$ is —$NH_2$. In some embodiments, $R_3$ is —CN. In some embodiments, $R_3$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_3$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_3$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_3$ is $C_2$-$C_6$ alkynyl.

**[0084]** In some embodiments, $R_3$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_7$. In some embodiments, $R_3$ is $C_1$-$C_6$ alkoxy optionally substituted with one or more $R_7$. In some embodiments, $R_3$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_7$. In some embodiments, $R_3$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_7$.

**[0085]** In some embodiments, Ra is independently at each occurrence H, halogen, —OH, —$NH_2$, —CN, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl. In some embodiments, $R_4$ is H. In some embodiments, $R_4$ is halogen. In some embodiments, $R_4$ is —OH. In some embodiments, R+is —$NH_2$. In some embodiments, $R_4$ is —CN. In some embodiments, $R_4$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_4$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_4$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_4$ is $C_2$-$C_6$ alkynyl.

**[0086]** In some embodiments, $R_4$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_7$. In some embodiments, $R_4$ is $C_1$-$C_6$ alkoxy optionally substituted with one or more $R_7$. In some embodiments, $R_4$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_7$. In some embodiments, $R_4$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_7$.

**[0087]** In some embodiments, $R_4$ and $R_9$ can form $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_4$ and $R_9$ can form $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0088]** In some embodiments, $R_4$ and $R_9$ can form $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_4$ and $R_9$ can form heterocyclyl. In some embodiments, $R_4$ and $R_9$ can form aryl. In some embodiments, $R_4$ and $R_9$ can form heteroaryl.

**[0089]** In some embodiments, $R_4$ and $R_9$ can form $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_4$ and $R_9$ can form heterocyclyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_4$ and $R_9$ can form aryl optionally substituted with one or more $R_{10}$. In some embodiments, $R_4$ and $R_9$ can form heteroaryl optionally substituted with one or more $R_{10}$.

**[0090]** In some embodiments, $R_5$ is H, halogen, —CN, —$OR_8$, —$NR_8R_9$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_7$.

**[0091]** In some embodiments, $R_5$ is H, halogen, —CN, —$OR_8$, —$NR_8R_9$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_5$ is H. In some embodiments, $R_5$ is halogen. In some embodiments, $R_5$ is CN. In some embodiments, $R_5$ is —$OR_8$. In some embodiments, $R_5$ is —$NR_8R_9$. In some embodiments, $R_5$ is —$C(O)R_8$. In some embodiments, $R_5$ is —$C(O)OR_8$. In some embodiments, $R_5$ is —$C(O)NR_8R_9$. In some embodiments, $R_5$ is —$NR_8C(O)R_9$. In some embodiments, $R_5$ is —$S(O)R_8$. In some embodiments, $R_5$ is —$S(O)_2R_8$. In some embodiments, $R_5$ is —$NR_8S(O)_2R_9$. In some embodiments, $R_5$ is —$S(O)_2NR_8R_9$. In some embodiments, $R_5$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_5$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_5$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_5$ is $C_2$-$C_6$ alkynyl. In some embodiments, $R_5$ is $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_5$ is heterocyclyl. In some embodiments, $R_5$ is aryl. In some embodiments, $R_5$ is heteroaryl.

**[0092]** In some embodiments, $R_5$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl.

**[0093]** In some embodiments, $R_5$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_5$ is methyl. In some embodiments, $R_5$ is ethyl. In some embodiments, $R_5$ is propyl. In some embodiments, $R_5$ is butyl. In some embodiments, $R_5$ is pentyl. In some embodiments, $R_5$ is hexyl.

**[0094]** In some embodiments, $R_5$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is methyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is ethyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is propyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is butyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is pentyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is hexyl optionally substituted with one or more $R_7$.

**[0095]** In some embodiments, $R_5$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_5$ is halomethyl. In some embodiments, $R_5$ is haloethyl. In some embodiments, $R_5$ is halopropyl. In some embodiments, $R_5$ is halobutyl. In some embodiments, $R_5$ is halopentyl. In some embodiments, $R_5$ is halohexyl.

**[0096]** In some embodiments, $R_5$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_5$ is $C_2$-$C_6$ alkynyl.

**[0097]** In some embodiments, $R_5$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_7$.

**[0098]** In some embodiments, $R_5$ is $C_3$-$C_{10}$ cycloalkyl.

**[0099]** In some embodiments, $R_5$ is $C_3$-$C_{10}$ cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more $R_7$.

**[0100]** In some embodiments, $R_5$ is $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_5$ is monocylic $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_5$ is bicyclic $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_5$ is polycyclic $C_3$-$C_{10}$ cycloalkyl.

**[0101]** In some embodiments, $R_5$ is $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_7$. In some embodi-

ments, $R_5$ is monocylic $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is bicyclic $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is polycyclic $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_7$.

**[0102]** In some embodiments, $R_5$ is heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_5$ is heterocyclyl. In some embodiments, $R_5$ is aryl. In some embodiments, $R_5$ is phenyl.

**[0103]** In some embodiments, $R_5$ is heterocyclyl, aryl, or heteroaryl, wherein the heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is heterocyclyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is aryl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is phenyl optionally substituted with one or more $R_7$.

**[0104]** In some embodiments, $R_5$ is heteroaryl. In some embodiments, $R_5$ is pyridine. In some embodiments, $R_5$ is imidazolyl. In some embodiments, $R_5$ is pyrazolyl. In some embodiments, $R_5$ is pyrimidinyl.

**[0105]** In some embodiments, $R_5$ is heteroaryl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is pyridine optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is imidazolyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is pyrazolyl optionally substituted with one or more $R_7$. In some embodiments, $R_5$ is pyrimidinyl optionally substituted with one or more $R_7$.

**[0106]** In some embodiments, $R_5$ is —$CF_3$. In some embodiments, $R_5$ is —$CHF_2$. In some embodiments, $R_5$ is —$CH_2F$.

**[0107]** In some embodiments, $R_6$ is independently at each occurrence oxo, halogen, —CN, OH, —$NR_8R_9$, —$OR_8$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_6$ is oxo. In some embodiments, $R_6$ is halogen. In some embodiments, $R_6$ is CN. In some embodiments, $R_6$ is OH. In some embodiments, $R_6$ is —$NR_8R_9$. In some embodiments, $R_6$ is —$OR_8$. In some embodiments, $R_6$ is —$NR_8R_9$. In some embodiments, $R_6$ is —$C(O)R_8$. In some embodiments, $R_6$ is —$C(O)OR_8$. In some embodiments, $R_6$ is —$C(O)NR_8R_9$. In some embodiments, $R_6$ is —$NR_8C(O)R_9$. In some embodiments, $R_6$ is —$S(O)R_8$. In some embodiments, $R_6$ is —$S(O)_2R_8$. In some embodiments, $R_6$ is —$NR_8S(O)_2R_9$. In some embodiments, $R_6$ is —$S(O)_2NR_8R_9$. In some embodiments, $R_6$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_6$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_6$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_6$ is $C_2$-$C_6$ alkynyl. In some embodiments, $R_6$ is $C_3$-$C_{10}$ cycloalkyl. In some embodiments, $R_6$ is heterocyclyl. In some embodiments, $R_6$ is aryl. In some embodiments, $R_6$ is heteroaryl.

**[0108]** In some embodiments, $R_6$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is $C_1$-$C_6$ haloalkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is $C_3$-$C_{10}$ cycloalkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is heterocyclyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is aryl optionally substituted with one or more $R_{10}$. In some embodiments, $R_6$ is heteroaryl optionally substituted with one or more $R_{10}$.

**[0109]** In another embodiment, two $R_6$ may combine to form $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In another embodiment, two $R_6$ may combine to form $C_3$-$C_{10}$ cycloalkyl. In another embodiment, two $R_6$ may combine to form a heteroaryl. In another embodiment, two $R_6$ may combine to form a heterocyclyl. In another embodiment, two $R_6$ may combine to form an aryl. In another embodiment, two $R_6$ may combine to form $C_3$-$C_{10}$ cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more $R_{10}$. In another embodiment, two $R_6$ may combine to form a heteroaryl, wherein the heteroaryl is optionally substituted with one or more $R_{10}$. In another embodiment, two $R_6$ may combine to form a heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more $R_{10}$. In another embodiment, two $R_6$ may combine to form an aryl wherein the aryl is optionally substituted with one or more $R_{10}$.

**[0110]** In some embodiments, $R_7$ is independently at each occurrence oxo, halogen, —CN, $OR_8$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, —$S(O)_2NR_8R_9$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0111]** In some embodiments, $R_7$ is independently at each occurrence oxo, halogen, or —CN. In some embodiments, $R_7$ is oxo. In some embodiments, $R_7$ is halogen. In some embodiments, $R_7$ is F, Cl, Br, or I. In some embodiments, $R_7$ is F or Cl. In some embodiments, $R_7$ is F. In some embodiments, $R_7$ is Cl. In some embodiments, $R_7$ is —CN.

**[0112]** In some embodiments, $R_7$ is independently at each occurrence —$OR_8$, —$C(O)R_8$, —$C(O)OR_8$, —$C(O)NR_8R_9$, —$NR_8C(O)R_9$, —$S(O)R_8$, —$S(O)_2R_8$, —$NR_8S(O)_2R_9$, or —$S(O)_2NR_8R_9$. In some embodiments, $R_7$ is —$OR_8$. In some embodiments, $R_7$ is —$C(O)R_8$. In some embodiments, $R_7$ is —$C(O)OR_8$. In some embodiments, $R_7$ is —$C(O)NR_8R_9$. In some embodiments, $R_7$ is —$NR_8C(O)R_9$. In some embodiments, $R_7$ is —$S(O)R_8$. In some embodiments, $R_7$ is —$S(O)_2R_8$. In some embodiments, $R_7$ is —$NR_8S(O)_2R_9$. In some embodiments, $R_7$ is —$S(O)_2NR_8R_9$.

**[0113]** In some embodiments, $R_7$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl.

**[0114]** In some embodiments, $R_7$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_7$ is methyl. In some embodiments, $R_7$ is ethyl. In some embodiments, $R_7$ is propyl. In some embodiments, $R_7$ is butyl. In some embodiments, $R_7$is pentyl. In some embodiments, $R_7$ is hexyl.

**[0115]** In some embodiments, $R_7$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_7$ is halomethyl. In some embodiments, $R_7$ is haloethyl. In some embodiments, $R_7$ is halopropyl. In some embodiments, $R_7$ is halobutyl. In some embodiments, $R_7$ is halopentyl. In some embodiments, $R_7$ is halohexyl.

**[0116]** In some embodiments, $R_7$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_7$ is $C_2$-$C_6$ alkynyl.

**[0117]** In some embodiments, $R_7$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl or heterocyclyl. In some embodiments, $R_7$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_7$ is heterocyclyl.

**[0118]** In some embodiments, $R_7$ is independently at each occurrence aryl or heteroaryl. In some embodiments, $R_7$ is aryl. In some embodiments, $R_7$ is heteroaryl.

**[0119]** In some embodiments, $R_8$ is independently at each occurrence H, OH, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0120]** In some embodiments, $R_9$ is independently at each occurrence H, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0121]** In some embodiments, $R_8$ and $R_9$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0122]** In some embodiments, $R_8$ and $R_9$ are independently at each occurrence H.

**[0123]** In some embodiments, $R_8$ and $R_9$ are independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0124]** In some embodiments, $R_8$ and $R_9$ are independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0125]** In some embodiments, $R_8$ is independently at each occurrence H, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0126]** In some embodiments, $R_8$ is independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0127]** In some embodiments, $R_8$ is H.

**[0128]** In some embodiments, $R_8$ is halogen.

**[0129]** In some embodiments, $R_8$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0130]** In some embodiments, $R_8$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0131]** In some embodiments, $R_8$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl.

**[0132]** In some embodiments, $R_8$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, wherein each alkyl, alkoxy, alkenyl or alkynyl is optionally substituted with one or more $R_{10}$.

**[0133]** In some embodiments, $R_8$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_8$ is methyl. In some embodiments, $R_8$ is ethyl. In some embodiments, $R_8$ is propyl. In some embodiments, $R_8$ is butyl. In some embodiments, $R_8$ is pentyl. In some embodiments, $R_8$ is hexyl.

**[0134]** In some embodiments, $R_8$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is methyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is ethyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is propyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is butyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is pentyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is hexyl optionally substituted with one or more $R_{10}$.

**[0135]** In some embodiments, $R_8$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_8$ is methoxy. In some embodiments, $R_8$ is ethoxy. In some embodiments, $R_8$ is propoxy. In some embodiments, $R_8$ is butoxy. In some embodiments, $R_8$ is pentoxy. In some embodiments, $R_8$ is hexoxy.

**[0136]** In some embodiments, $R_8$ is $C_1$-$C_6$ alkoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is methoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is ethoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is propoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is butoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is pentoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is hexoxy optionally substituted with one or more $R_{10}$.

**[0137]** In some embodiments, $R_8$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_8$ is $C_2$-$C_6$ alkynyl.

**[0138]** In some embodiments, $R_8$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_{10}$.

**[0139]** In some embodiments, $R_8$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0140]** In some embodiments, $R_8$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0141]** In some embodiments, $R_8$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_8$ is heterocyclyl. In some embodiments, $R_8$ is aryl. In some embodiments, $R_8$ is heteroaryl.

**[0142]** In some embodiments, $R_8$ is $C_3$-$C_8$ cycloalkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is heterocyclyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is aryl optionally substituted with one or more $R_{10}$. In some embodiments, $R_8$ is heteroaryl optionally substituted with one or more $R_{10}$.

**[0143]** In some embodiments, $R_9$ is independently at each occurrence H, halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0144]** In some embodiments, $R_9$ is independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0145]** In some embodiments, $R_9$ is H.

**[0146]** In some embodiments, $R_9$ is halogen.

**[0147]** In some embodiments, $R_9$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0148]** In some embodiments, $R_9$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl,

wherein each alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0149]** In some embodiments, $R_9$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl.

**[0150]** In some embodiments, $R_9$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, wherein each alkyl, alkoxy, alkenyl, or alkynyl is optionally substituted with one or more $R_{10}$.

**[0151]** In some embodiments, $R_9$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_9$ is methyl. In some embodiments, Ro is ethyl. In some embodiments, $R_9$ is propyl. In some embodiments, $R_9$ is butyl. In some embodiments, $R_9$ is pentyl. In some embodiments, $R_9$ is hexyl.

**[0152]** In some embodiments, $R_9$ is $C_1$-$C_6$ alkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is methyl optionally substituted with one or more $R_{10}$. In some embodiments, Ro is ethyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is propyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is butyl optionally substituted with one or more $R_{10}$. In some embodiments, Ro is pentyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is hexyl optionally substituted with one or more $R_{10}$.

**[0153]** In some embodiments, $R_9$ is $C_1$-$C_6$ alkoxy. In some embodiments, $R_9$ is methoxy. In some embodiments, $R_9$ is ethoxy. In some embodiments, $R_9$ is propoxy. In some embodiments, $R_9$ is butoxy. In some embodiments, $R_9$ is pentoxy. In some embodiments, $R_9$ is hexoxy.

**[0154]** In some embodiments, $R_9$ is $C_1$-$C_6$ alkoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is methoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is ethoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is propoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is butoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is pentoxy optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is hexoxy optionally substituted with one or more $R_{10}$.

**[0155]** In some embodiments, $R_9$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_9$ is $C_2$-$C_6$ alkynyl.

**[0156]** In some embodiments, $R_9$ is $C_2$-$C_6$ alkenyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is $C_2$-$C_6$ alkynyl optionally substituted with one or more $R_{10}$.

**[0157]** In some embodiments, $R_9$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0158]** In some embodiments, $R_9$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more $R_{10}$.

**[0159]** In some embodiments, $R_9$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_9$ is heterocyclyl. In some embodiments, $R_9$ is aryl. In some embodiments, $R_9$ is heteroaryl.

**[0160]** In some embodiments, $R_9$ is $C_3$-$C_8$ cycloalkyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is heterocyclyl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is aryl optionally substituted with one or more $R_{10}$. In some embodiments, $R_9$ is heteroaryl optionally substituted with one or more $R_{10}$.

**[0161]** In some embodiments, $R_8$ and $R_9$ when taken together form a $C_3$-$C_6$ cycloalkyl or heterocycle, wherein the cycloalkyl or heterocycle is optionally substituted with $R_{10}$.

**[0162]** In some embodiments, $R_8$ and $R_9$ when taken together form a $C_3$-$C_6$ cycloalkyl, wherein the cycloalkyl is optionally substituted with $R_{10}$. In some embodiments, $R_8$ and $R_9$ when taken together form a $C_3$-$C_6$ cycloalkyl. In some embodiments, $R_8$ and $R_9$ when taken together form cyclopropyl, wherein the cyclopropyl is optionally substituted with $R_{10}$. In some embodiments, $R_8$ and $R_9$ when taken together form cyclopropyl.

**[0163]** In some embodiments, $R_8$ and $R_9$ when taken together form a heterocycle, wherein the heterocycle is optionally substituted with $R_{10}$. In some embodiments, $R_8$ and $R_9$ when taken together form a 4-membered heterocycle optionally substituted with $R_{10}$. In some embodiments, $R_8$ and $R_9$ when taken together form azetidinyl optionally substituted with $R_{10}$. In some embodiments, $R_8$ and $R_9$ when taken together form oxetanyl optionally substituted with $R_{10}$.

**[0164]** In some embodiments, $R_{10}$ is independently at each occurrence oxo, halogen, —CN, —$OR_{11}$, —$C(O)R_{11}$, —$C(O)OR_{11}$, —$C(O)NR_{11}R_{12}$, —$NR_{11}C(O)R_{12}$, —$S(O)R_{11}$, —$S(O)_2R_{11}$, —$NR_{11}S(O)_2R_{12}$, —$S(O)_2NR_{11}R_{12}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0165]** In some embodiments, $R_{10}$ is independently at each occurrence oxo, halogen, —CN, —$OR_{11}$, —$C(O)R_{11}$, —$C(O)OR_{11}$, —$C(O)NR_{11}R_{12}$, —$NR_{11}R_{12}$, —$NR_{11}C(O)R_{12}$, —$S(O)R_{11}$, —$S(O)_2R_{11}$, —$NR_{11}S(O)_2R_{12}$, —$S(O)_2NR_{11}R_{12}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0166]** In some embodiments, $R_{10}$ is independently at each occurrence oxo, halogen, or —CN. In some embodiments, $R_{10}$ is oxo. In some embodiments, $R_{10}$ is halogen. In some embodiments, $R_{10}$ is F, Cl, Br, or I. In some embodiments, $R_{10}$ is F or Cl. In some embodiments, $R_{10}$ is F. In some embodiments, $R_{10}$ is Cl. In some embodiments, $R_{10}$ is —CN.

**[0167]** In some embodiments, $R_{10}$ is independently at each occurrence —$OR_{11}$, —$C(O)R_{11}$, —$C(O)OR_{11}$, —$C(O)NR_{11}R_{12}$, —$NR_{11}C(O)R_{12}$, —$S(O)R_{11}I$, —$S(O)_2R_{11}$, —$NR_{11}S(O)_2R_{12}$, or —$S(O)_2NR_{11}R_{12}$. In some embodiments, $R_{10}$ is —$OR_{11}$. In some embodiments, $R_{10}$ is —$C(O)R_{11}$. In some embodiments, $R_{10}$ is —$C(O)OR_{11}$. In some embodiments, $R_{10}$ is —$C(O)NR_{11}R_{12}$. In some embodiments, $R_{10}$ is —$NR_{11}C(O)R_{12}$. In some embodiments, $R_{10}$ is —$S(O)R_{11}$. In some embodiments, $R_{10}$ is —$S(O)_2R_{11}$. In some embodiments, $R_{10}$ is —$NR_{11}IS(O)_2R_{12}$. In some embodiments, $R_{10}$ is —$S(O)_2NR_{11}R_{12}$.

**[0168]** In some embodiments, $R_{10}$ is independently at each occurrence $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl.

**[0169]** In some embodiments, $R_{10}$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_{10}$ is methyl. In some embodiments, $R_{10}$ is ethyl. In some embodiments, $R_{10}$ is propyl. In some embodiments, $R_{10}$ is butyl. In some embodiments, $R_{10}$ is pentyl. In some embodiments, $R_{10}$ is hexyl.

**[0170]** In some embodiments, $R_{10}$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_{10}$ is halomethyl. In some embodiments, $R_{10}$ is haloethyl. In some embodiments, $R_{10}$ is halopropyl. In some embodiments, $R_{10}$ is halobutyl. In some embodiments, $R_{10}$ is halopentyl. In some embodiments, $R_{10}$ is halohexyl.

**[0171]** In some embodiments, $R_{10}$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_{10}$ is $C_2$-$C_6$ alkynyl.

**[0172]** In some embodiments, $R_{10}$ is independently at each occurrence $C_3$-$C_8$ cycloalkyl or heterocyclyl. In some embodiments, $R_{10}$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_{10}$ is heterocyclyl.

**[0173]** In some embodiments, $R_{10}$ is independently at each occurrence aryl or heteroaryl. In some embodiments, $R_{10}$ is aryl. In some embodiments, $R_{10}$ is heteroaryl.

**[0174]** In some embodiments, $R_{10}$ is —OH.

**[0175]** In some embodiments, $R_{11}$ and $R_{12}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0176]** In some embodiments, $R_{11}$ and $R_{12}$ are independently H.

**[0177]** In some embodiments, $R_{11}$ and $R_{12}$ are independently $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0178]** In some embodiments, $R_{11}$ is H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0179]** In some embodiments, $R_{11}$ is H.

**[0180]** In some embodiments, $R_{11}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0181]** In some embodiments, $R_{11}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl.

**[0182]** In some embodiments, $R_{11}$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_{11}$ is methyl. In some embodiments, $R_{11}$ is ethyl. In some embodiments, $R_{11}$ is propyl. In some embodiments, $R_{11}$ is butyl. In some embodiments, $R_{11}$ is pentyl. In some embodiments, $R_{11}$ is hexyl.

**[0183]** In some embodiments, $R_{11}$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_{11}$ is halomethyl. In some embodiments, $R_{11}$ is haloethyl. In some embodiments, $R_{11}$ is halopropyl. In some embodiments, $R_{11}$ is halobutyl. In some embodiments, $R_{11}$ is halopentyl. In some embodiments, $R_{11}$ is halohexyl.

**[0184]** In some embodiments, $R_{11}$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_{11}$ is $C_2$-$C_6$ alkynyl.

**[0185]** In some embodiments, $R_{11}$ is $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_{11}$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_{11}$ is heterocyclyl. In some embodiments, $R_{11}$ is aryl. In some embodiments, $R_{11}$ is heteroaryl.

**[0186]** In some embodiments, $R_{12}$ is H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0187]** In some embodiments, $R_{12}$ is H.

**[0188]** In some embodiments, $R_{12}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0189]** In some embodiments, $R_{12}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl.

**[0190]** In some embodiments, $R_{12}$ is $C_1$-$C_6$ alkyl. In some embodiments, $R_{12}$ is methyl. In some embodiments, $R_{12}$ is ethyl. In some embodiments, $R_{12}$ is propyl. In some embodiments, $R_{12}$ is butyl. In some embodiments, $R_{12}$ is pentyl. In some embodiments, $R_{12}$ is hexyl.

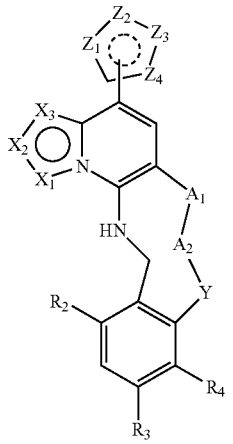
**[0191]** In some embodiments, $R_{12}$ is $C_1$-$C_6$ haloalkyl. In some embodiments, $R_{12}$ is halomethyl. In some embodiments, $R_{12}$ is haloethyl. In some embodiments, $R_{12}$ is halopropyl. In some embodiments, $R_{12}$ is halobutyl. In some embodiments, $R_{12}$ is halopentyl. In some embodiments, $R_{12}$ is halohexyl.

**[0192]** In some embodiments, $R_{12}$ is $C_2$-$C_6$ alkenyl. In some embodiments, $R_{12}$ is $C_2$-$C_6$ alkynyl.

**[0193]** In some embodiments, $R_{12}$ is $C_3$-$C_8$ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, $R_{12}$ is $C_3$-$C_8$ cycloalkyl. In some embodiments, $R_{12}$ is heterocyclyl. In some embodiments, $R_{12}$ is aryl. In some embodiments, $R_{12}$ is heteroaryl.

**[0194]** In some embodiments, the compounds of the present disclosure are represented by compounds of Formula II:

(II)

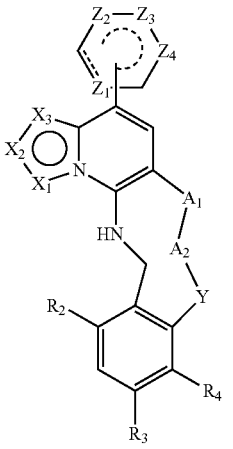



or pharmaceutically acceptable salts, prodrugs, solvates, hydrates, enantiomers, isomers, or tautomers thereof, wherein:

**[0195]** ------ represents optional double bonds which can form an aromatic when present; $Z_1$, $Z_2$, $Z_3$, and $Z_4$ are independently C, N, S, O, N($R_{10}$), or C($R_{10}$); and $X_1$, $X_2$, $X_3$, $A_1$, $A_2$, Y, $R_2$, $R_3$, $R_4$, $R_{10}$ are described as herein.

**[0196]** In some embodiments, the compounds of the present disclosure are represented by compounds of Formula III:

(III)



or pharmaceutically acceptable salts, prodrugs, solvates, hydrates, enantiomers, isomers, or tautomers thereof,

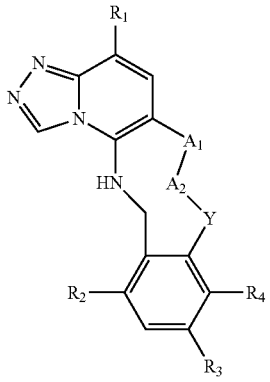
wherein:

**[0197]** ------ straight or curved represents optional double bonds that form a partially unsaturated ring or an aromatic ring when present;

**[0198]** $Z_1$, $Z_2$, $Z_3$, and $Z_4$ are independently C, N, O, $N(R_{10})$, or $C(R_{10})$, provided $Z_1$, $Z_2$, $Z_3$, and $Z_4$ are not all N or $N(R_{10})$ when ------ is present and aromatic; provided that no three N or $N(R_{10})$ are adjacent; provided that $Z_1$, $Z_2$, $Z_3$, and $Z_4$ are not O when ------ is present and aromatic; and $X_1$, $X_2$, $X_3$, $A_1$, $A_2$, Y, $R_2$, $R_3$, $R_4$, $R_{10}$ are described as herein.

**[0199]** In some embodiments, the compound is of formula Ia:

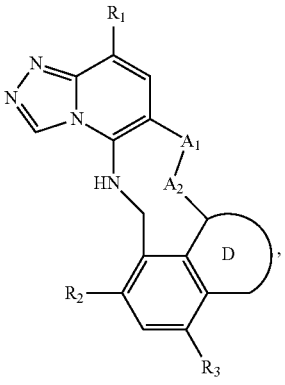
(Ia)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

**[0200]** In some embodiments, the compound is of formula Ib:

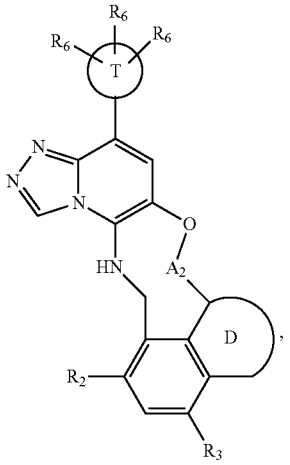
(Ib)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the D ring represents a $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

**[0201]** In some embodiments, the compound is of formula Ic:

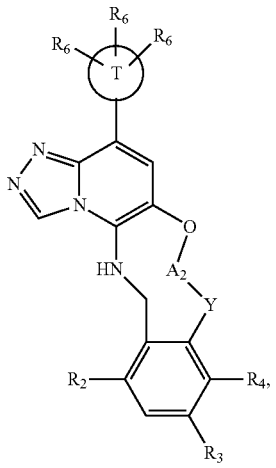
(Idc)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the D ring represents a $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl; and the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0202]** In some embodiments, the compound is of formula Id:

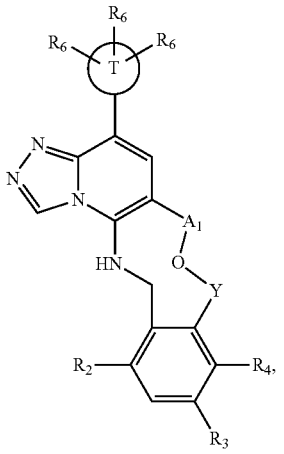
(Id)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0203]** In some embodiments, the compound is of formula Ie:

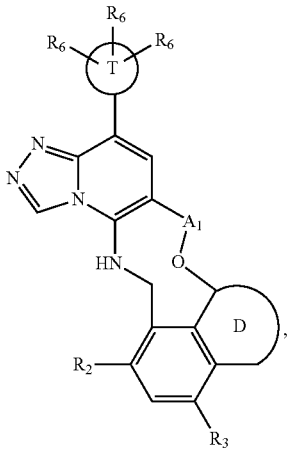
(Ie)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0204]** In some embodiments, the compound is of formula If;

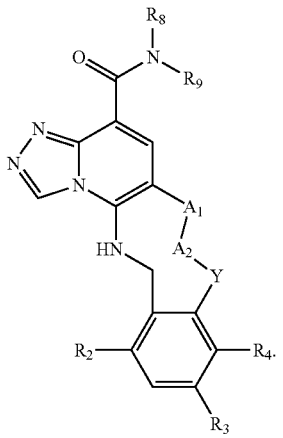
(If)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the D ring represents a $C_3$-$C_{10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl; and the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0205]** In some embodiments, the compound is of formula Ig:

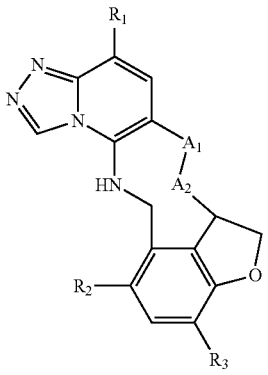
(Ig)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

**[0206]** In some embodiments, the compound is of formula Ih:

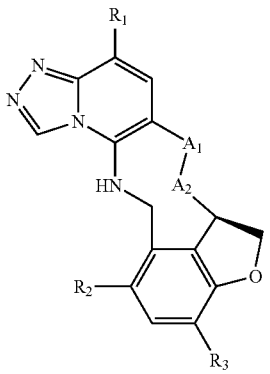
(Ih)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

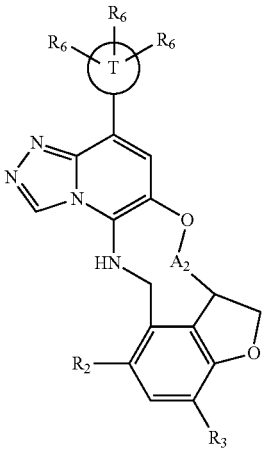
**[0207]** In some embodiments, the compound is of formula Ih-a:

(Ih-a)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

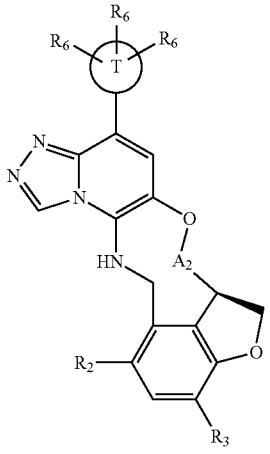
**[0208]** In some embodiments, the compound is of formula Ii:



(Ii)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0209]** In some embodiments, the compound is of formula Ii-a:



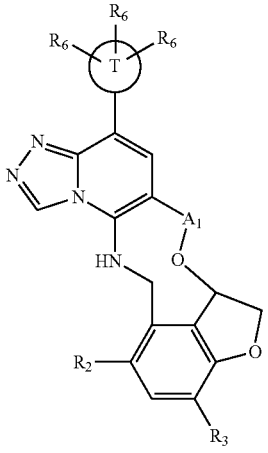
(Ii-a)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0210]** In some embodiments, the compound is of formula Ii or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a heterocyclyl.

**[0211]** In some embodiments, the compound is of formula Ii-a or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a heterocyclyl.

**[0212]** In some embodiments, the compound is of formula Ij:

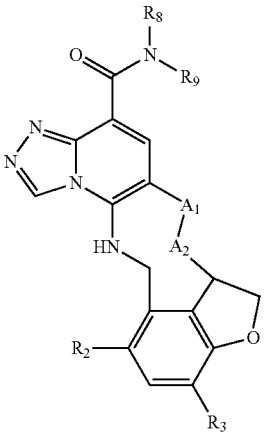


(Ij)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_8$ spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl.

**[0213]** In some embodiments, the compound is of formula Ij or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, wherein the T ring represents a heterocyclyl.

**[0214]** In some embodiments, the compound is of formula Ik:

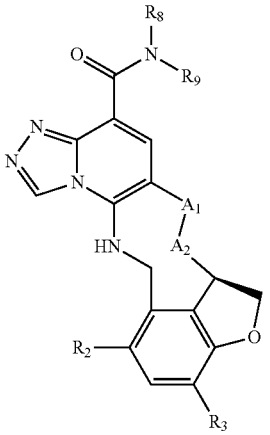


(Ik)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

**[0215]** In some embodiments, the compound is of formula Ik-a:

(Ik-a)



or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof.

**[0216]** In some embodiments, inhibitors of the disclosure are and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, enantiomers, isomers, and tautomers thereof are described in Table 1.

TABLE 1

| Compound No. | Compound Name |
|---|---|
| 1 | (15R)-10-(2-methyl-3-pyridyl)-13,17-dioxa-3,5,7,8-tetrazapentacyclo [13.6.1.04,12.05,9.018,22] docosa-1(22),4(12),6,8,10,18,20-heptaene |
| 3 | (S)-1-(4-(7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)piperidin-1-yl)ethan-1-one |
| 4 | 1-(4-(12-fluoro-7,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzo[f][1,4]oxazonin-4-yl)piperidin-1-yl)ethan-1-one |
| 5 | 12-fluoro-4-(2-methylpyridin-3-yl)-7,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzo[f][1,4]oxazonine |
| 6 | 12-fluoro-4-(2-methylpyridin-3-yl)-6,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-c]benzo[g][1,5]oxazonine |
| 7 | (S)-4-((1-methyl-1H-pyrazol-4-yl)methyl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 8 | (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 9 | (S)-1-(4-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)piperidin-1-yl)ethan-1-one |
| 10 | (S)-12-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methyl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 11 | (S)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 12 | (S)-12-fluoro-4-(oxetan-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 13 | (S)-4-(2,4-dimethylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 14 | 4-(2,4-dimethylpyrimidin-5-yl)-12-fluoro-7,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzo[f][1,4]oxazonine |
| 15 | (S)-12-fluoro-4-(4-methyl-1H-imidazol-1-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 16 | methyl (S)-4-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)piperidine-1-carboxylate |
| 17 | (S)-12-fluoro-4-(1-methyl-1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 18 | (S)-4-(1,3-dimethyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 19 | (S)-12-fluoro-4-(4-methylpyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 20 | (S)-12-fluoro-4-(2-methylpyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 21 | (S)-12-fluoro-4-(pyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 22 | (S)-4-(1,3-dimethyl-1H-pyrazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |

TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 23 | (S)-4-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 24 | (S)-4-((S)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methylpiperidin-2-one |
| 25 | (R)-4-((S)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methylpiperidin-2-one |
| 26 | (S)-4-ethyl-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 27 | (S)-12-fluoro-4-(1H-pyrazol-1-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 28 | (S)-4-(1,5-dimethyl-1H-pyrazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 29 | (S)-4-(2,3-dimethylpyridin-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 30 | (S)-12-fluoro-4-(2-methoxypyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 31 | (S)-12-fluoro-4-(6-methoxypyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 32 | (S)-4-(6-ethyl-4-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 33 | (S)-4-(2-(difluoromethyl)pyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 34 | (S)-4-(2,6-dimethylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 35 | (S)-2-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)pyridin-2-yl)propan-2-ol |
| 36 | (S)-12-fluoro-4-(4-(methylsulfonyl)phenyl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 37 | (S)-12-fluoro-N,N-dimethyl-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine-4-carboxamide |
| 38 | (S)-12-fluoro-N-methyl-N-(2,2,2-trifluoroethyl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine-4-carboxamide |
| 39 | (S)-12-fluoro-4-(1-methyl-1H-pyrazol-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 40 | (S)-12-fluoro-4-(5-fluoro-2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 41 | (S)-12-fluoro-4-(3-fluoropyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 42 | (S)-12-fluoro-4-(5-fluoropyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 43 | (S)-12-fluoro-4-(3-fluoro-5-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 44 | (S)-4-(3,5-difluoropyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 45 | (S)-12-fluoro-4-(5-fluoro-3-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 46 | (S)-12-fluoro-4-(5-methylpyrazin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 47 | (S)-12-fluoro-4-(3-methylpyrazin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 48 | (S)-4-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)benzonitrile |
| 49 | (S)-4-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-3-methylbenzonitrile |
| 50 | (S)-12-fluoro-4-(2-methoxypyridin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 51 | (S)-3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-2-methylpyridine 1-oxide |
| 52 | (S)-4-(3,5-dimethylpyrazin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 53 | (S)-12-fluoro-4-(3-methylpyridazin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 54 | (S)-12-fluoro-4-(4-methylpyridazin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 55 | (S)-12-fluoro-4-(6-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 56 | (S)-12-fluoro-4-(2-methylpyrimidin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 57 | (S)-12-fluoro-4-(2-methoxy-4-methylpyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |

TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 58 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,N,4-trimethylpyrimidine-2-carboxamide |
| 59 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,N-dimethylpicolinamide |
| 60 | (S)-4-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 61 | (S)-12-fluoro-4-(5-methyl-1,3,4-oxadiazol-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 62 | (S)-4-(3,5-dimethylisoxazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 63 | (S)-12-fluoro-4-(1-(2-methoxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 64 | (S)-12-fluoro-N-methyl-N-(tetrahydro-2H-pyran-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine-4-carboxamide |
| 65 | (S)-12-fluoro-4-(5-methylpyrimidin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 66 | (S)-12-fluoro-4-(6-methylpyridazin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 67 | (S)-4-(4,6-dimethylpyridazin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 68 | (S)-4-(4-(difluoromethyl)-2-methylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 69 | (S)-4-(2-(difluoromethyl)-4-methylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 70 | (S)-4-(4-(difluoromethyl)pyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 71 | (S)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 72 | (S)-4-(1-ethyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 73 | (S)-12-fluoro-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 74 | (S)-1-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol |
| 75 | (S)-12-fluoro-4-(1-isopropyl-1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 76 | (S)-4-(2-(difluoromethoxy)pyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 77 | (S)-12-fluoro-4-(2-methoxypyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 78 | (S)-4-(2-(difluoromethoxy)pyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 79 | (S)-12-fluoro-4-(3-methyl-1H-pyrazol-1-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 80 | (S)-12-fluoro-4-(4-methyl-1H-pyrazol-1-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 81 | (S)-1-(3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)pyridin-2-yl)-2-methylpropan-2-ol |
| 82 | (S)-4-(3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)pyridin-2-yl)-2-methylbutan-2-ol |
| 83 | (S)-12-fluoro-4-(2-(trifluoromethoxy)pyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 84 | (S)-4-(6-(difluoromethyl)-2-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 85 | (S)-4-(2-(difluoromethyl)-6-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 86 | (S)-4-(4,6-dimethylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 87 | (S)-12-fluoro-4-(3-fluoro-2-methylpyridin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 88 | (S)-4-(4-(difluoromethyl)-6-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 89 | (S)-12-fluoro-4-(5-fluoro-2-methylpyridin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 90 | (S)-4-(6-(difluoromethyl)-4-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |

TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 91 | (S)-12-fluoro-4-(pyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 92 | (S)-12-fluoro-4-(3-methylisoxazol-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 93 | (S)-12-fluoro-4-(thiazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 94 | (S)-12-fluoro-4-(6-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 95 | (S)-12-fluoro-4-(3-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 96 | (S)-4-(2-ethylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 97 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methylpyridin-2(1H)-one |
| 98 | (S)-12-fluoro-4-(6-methoxypyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 99 | (S)-12-fluoro-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 100 | (S)-4-(3-ethyl-1-methyl-1H-pyrazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 101 | (S)-4-(5-chloropyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 102 | (S)-4-(4-cyclopropylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 103 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,N-dimethylpyridin-2-amine |
| 104 | (S)-12-fluoro-4-(6-methoxy-4-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 105 | (S)-12-fluoro-4-(2-methoxy-6-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 106 | (S)-12-fluoro-4-(6-methoxy-2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 107 | (S)-12-fluoro-4-(2-methoxy-4-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 108 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,N-dimethylpyrimidin-2-amine |
| 109 | (S)-4-(2-ethoxypyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 110 | (S)-12-fluoro-4-(5-fluoro-6-methoxypyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 111 | (S)-12-fluoro-4-(5-fluoro-2-methoxypyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 112 | (S)-12-fluoro-4-(6-(trifluoromethyl)pyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 113 | (S)-12-fluoro-4-(5-(trifluoromethyl)pyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 114 | (S)-12-fluoro-4-(2-(trifluoromethyl)pyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 115 | (S)-12-fluoro-4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 116 | (S)-12-fluoro-4-(6-morpholinopyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 117 | (S)-12-fluoro-4-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 118 | (S)-12-fluoro-4-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 119 | (S)-12-fluoro-4-(2-(trifluoromethyl)pyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 120 | (S)-12-fluoro-4-(5-fluoro-6-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 121 | (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[r,5':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 122 | (S)-12-fluoro-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 123 | (S)-12-fluoro-4-(6-methylpyridazin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 124 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-amine |
| 125 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,1-dimethyl-1H-pyrazol-3-amine |
| 126 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-N,N,1-trimethyl-1H-pyrazol-3-amine |

TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 127 | (S)-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)methanamine |
| 128 | (S)-1-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)-N-methylmethanamine |
| 129 | (S)-1-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)-N,N-dimethylmethanamine |
| 130 | (S)-4-(3-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 131 | (S)-2-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)ethan-1-ol |
| 132 | (S)-2-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)-N,N-dimethylethan-1-amine |
| 133 | (S)-4-(1,2-dimethyl-1H-imidazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 134 | (S)-4-(1,4-dimethyl-1H-imidazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 135 | (S)-4-(1,4-dimethyl-1H-imidazol-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 136 | (S)-4-(1,5-dimethyl-1H-imidazol-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 137 | (S)-12-fluoro-4-(1-methyl-1H-imidazol-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 138 | (S)-12-fluoro-4-(1-methyl-1H-imidazol-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 139 | (S)-4-(1,5-dimethyl-1H-imidazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 140 | (S)-4-(1,2-dimethyl-1H-imidazol-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 141 | (S)-4-(5-(difluoromethyl)-6-methylpyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 142 | (S)-12-fluoro-4-(1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 143 | (S)-1-(3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol |
| 144 | (S)-4-(3-(difluoromethyl)-6-methylpyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 145 | (S)-4-(3-ethyl-1-methyl-1H-1,2,4-triazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 146 | (S)-4-(3-ethyl-1-methyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 147 | (S)-12-fluoro-4-(1,2,4-trimethyl-1H-imidazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 148 | (S)-12-fluoro-4-(1,4,5-trimethyl-1H-imidazol-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 149 | (S)-12-fluoro-4-(4-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 150 | (S)-12-fluoro-4-(5-methylpyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 151 | (S)-4-(3-chloropyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 152 | (S)-4-(5-chloro-2-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 153 | (S)-4-(5-chloro-6-methylpyridin-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 154 | (S)-12-fluoro-4-(5-fluoro-6-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 155 | (S)-12-fluoro-4-(2-methylpyridin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 156 | (S)-4-(2,5-dimethylpyridin-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 157 | (S)-4-(3-chloro-2-methylpyridin-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 158 | (S)-4-(3-chloro-5-fluoropyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 159 | (S)-12-fluoro-4-(3-methoxypyridin-2-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 160 | (S)-12-fluoro-4-(pyrimidin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |

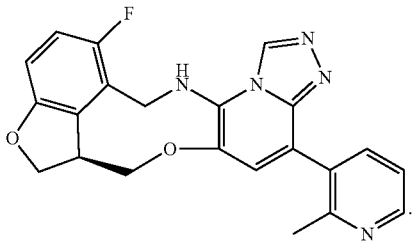
TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 161 | (S)-12-fluoro-4-(6-methylpyrimidin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 162 | (S)-12-fluoro-4-(5-methylpyrimidin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 163 | (S)-4-(5-chloropyrimidin-4-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 164 | (S)-12-fluoro-4-(5-fluoropyrimidin-4-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 165 | (S)-4-bromo-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 166 | (S)-4-(5-chloro-3-methylpyridin-2-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 167 | (S)-4-(3-(difluoromethoxy)-1-methyl-1H-pyrazol-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 168 | (S)-12-fluoro-4-(3-fluoro-1-methyl-1H-pyrazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 169 | (S)-2-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-yl)-2-methylpropanenitrile |
| 170 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazole-4-carbonitrile |
| 171 | (S)-4-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 172 | (S)-5-fluoro-12-(1-methyl-1H-pyrazol-5-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[r,2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carbonitrile |
| 174 | (S)-5-fluoro-12-(1-methyl-1H-pyrazol-5-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[r,2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carboxylic acid |
| 175 | (S)-5-fluoro-12-(1-methyl-1H-pyrazol-5-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[r,2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carboxamide |
| 176 | (S)-5-fluoro-12-(2-methylpyridin-3-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[r,2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carboxamide |
| 177 | (S)-5-fluoro-12-(2-methylpyridin-3-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[r,2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carboxylic acid |
| 178 | (S)-4-(2-cyclopropylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 179 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-2-methylpyridin-3-amine |
| 181 | methyl 4-(12-fluoro-6,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-c]benzo[g][1,5]oxazonin-4-yl)piperidine-1-carboxylate |
| 182 | 4-(2,4-dimethylpyrimidin-5-yl)-12-fluoro-6,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-c]benzo[g][1,5]oxazonine |
| 183 | 12-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methyl)-6,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-c]benzo[g][1,5]oxazonine |
| 184 | (S)-4-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 185 | (R)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 186 | (S)-5-fluoro-12-(2-methylpyridin-3-yl)-6,7,15,15a-tetrahydro-1H-benzofuro[4,3-fg]imidazo[1',2':1,6]pyrido[3,2-b][1,4]oxazonine-10-carbonitrile |
| 187 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-6-methylpyridin-2-ol |
| 188 | (S)-12-fluoro-4-(oxazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 189 | (S)-12-fluoro-4-(4-methyloxazol-5-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 190 | (S)-4-(2-cyclopropyl-4-methylpyrimidin-5-yl)-12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine |
| 191 | (S)-3-(5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-6-methylpyridin-2-yl)-N-methylpropanamide |
| 192 | (S)-3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-2-methylpyridin-4-ol |
| 193 | (S)-1-(4-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-3,6-dihydropyridin-1(2H)-yl)ethan-1-one |
| 194 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-6-methylpyridin-3-ol |
| 195 | (S)-(3-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)pyridin-2-yl)methanol |
| 196 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-4-ol |
| 197 | (S)-5-(12-fluoro-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonin-4-yl)-1-methyl-1H-pyrazol-3-ol |

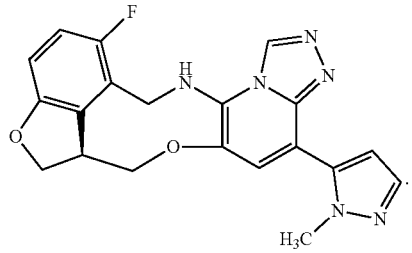
TABLE 1-continued

| Compound No. | Compound Name |
|---|---|
| 198 | 1-(4-(12-fluoro-6,8,13,14-tetrahydro-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-c]benzo[g][1,5]oxazonin-4-yl)piperidin-1-yl)ethan-1-one |

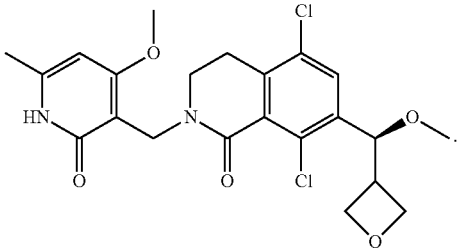
**[0217]** In some embodiments, the compound is:



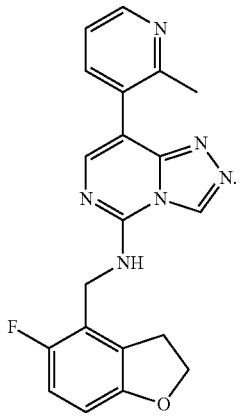
**[0218]** In some embodiments, the compound is:



**[0219]** In some embodiments, the inhibitor is:



**[0220]** In some embodiments, the inhibitor is:



**[0221]** Additional inhibitors useful in the methods of the present disclosure include, but are not limited to, tazemetostat, CPI-0209, CPI-1205, EBI-2554, HH-2853, MAK-683, SHR-2554, valemetostat, PF-06821497, ORIC-944, and GSK-2816126.

## Alternative Embodiments

**[0222]** In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be 2H (D or deuterium) or 3H (T or tritium); carbon may be, for example, 13C or 14C; oxygen may be, for example, 180; nitrogen may be, for example, 15N, and the like. In other embodiments, a particular isotope (e.g., 3H, 13C, 14C, 180, or 15N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

## EXAMPLES

**[0223]** Abbreviations: DMSO: dimethyl sulfoxide; EPO: erythropoietin; FPKM: fragments per kilobase of transcript per million mapped reads; HbA: hemoglobin A; HbC: hemoglobin C; HbF: fetal hemoglobin; HbS: hemoglobin S; HPLC: high-performance liquid chromatography; hSCF: human stem cell factor; IMDM: Iscove's Modified Dulbecco's Medium.

### Example 1. Compound 1 Decreases BCL11A mRNA Expression

**[0224]** Human Mobilized Peripheral Blood Primary CD34+ cells from healthy donors were expanded from thaw by seeding 100,000 viable cells/mL in a culture flask containing CD34+ Phase 1 Media comprised of IMDM, 100 ng/ml hSCF, 5 ng/ml IL-3, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin. The cells were supplemented by adding an additional 1X culture volume of CD34+ Phase 1 Media on Day 3 after thaw. At Day 7 post-thaw, cells were seeded at 0.111×10^6 cells/ml in 1.5 mLs of Phase 1 media in 12-well plates and compound was applied. On Day 10 post-thaw, cells were differentiated towards the erythroid lineage by complete medium exchange into CD34+ Phase 2 Media comprised of IMDM, 100 ng/ml hSCF, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/mL heparin, 10 μg/mL insulin and compound treatment was reapplied. On Day 12 post-thaw the plates were centrifuged, and 1 mL of Phase 2 media exchanged with fresh Phase 2 media and compound. The cells were harvested on Day 14 post-thaw for downstream analyses.

**[0225]** RNA was extracted from Day 14 post-thaw primary CD34+ cells that were differentiated and treated for 7 days with DMSO, 11 nM, 33 nM, 100 nM, or 300 nM of Compound 1 using Ambion mirVana RNA extraction kits. Purified RNA samples were submitted for library preparation and deep sequencing at Novogene. Sequenced raw reads of fastq files from all samples were mapped to hg38 genome assemblies using ArrayStudio aligner. Raw read counts and FPKM were calculated for all genes and DESeq2 was applied to calculate differentially expressed genes using general linear model. The statistical cutoff of absolute fold change greater than 4 (fdr<0.05, abs(FC)>4, log2(FPKM+1)>1).

**[0226]** BCL11A mRNA decreased in a concentration dependent manner with Compound 1 challenge, as depicted in FIG. **1**. For example, 100 nM Compound 1 significantly decreased BCL11A mRNA levels relative to DMSO and other HbF inducing mechanisms.

Example 2. EED Inhibitors Decrease BCL11A Expression, Increase HBG1 Expression, and Increase HBG2 Expression in Multiple Healthy CD34+ Donor Cells

**[0227]** Changes in BCL11A expression and HBG1 and HBG2 expression in multiple healthy CD34+ donor cells were measured by RNA sequencing (RNA-Seq). Human Mobilized Peripheral Blood Primary CD34+ cells from 2 healthy donors and 1 sickle cell trait donor were expanded from thaw by seeding 100,000 viable cells/mL in a culture flask containing CD34+ Phase 1 Media comprised of IMDM, 100 ng/ml hSCF, 5 ng/ml IL-3, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin. The cells were supplemented by adding an additional 1X culture volume of CD34+ Phase 1 Media on Day 3 after thaw. At Day 7 post-thaw, cells were seeded at 0.111×10^6 cells/ml in 1.5 mLs of Phase 1 media in 12-well plates and compound was applied. On Day 10 post-thaw, cells were differentiated towards the erythroid lineage by complete medium exchange into CD34+ Phase 2 Media comprised of IMDM, 100 ng/ml hSCF, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin and compound treatment was reapplied. On Day 12 post-thaw the plates were centrifuged, and 1 mL of Phase 2 media exchanged with fresh Phase 2 media and compound. The cells were harvested on Day 14 post-thaw for downstream analyses.

**[0228]** RNA was extracted from Day 14 post-thaw primary CD34+ cells that were differentiated and treated for 7 days with DMSO, 100 nM of Compound 1, or 100 nM of Compound 2 using Ambion mirVana RNA extraction kits. Purified RNA samples were submitted for library preparation and deep sequencing at Novogene. Sequenced raw reads of fastq files from all samples were mapped to hg38 genome assemblies using ArrayStudio aligner. Raw read counts and FPKM were calculated for all genes and DESeq2 was applied to calculate differentially expressed genes using general linear model. The statistical cutoff of absolute fold change greater than 4 (fdr<0.05, abs(FC)>4, log2(FPKM+1)>1).

**[0229]** Hemoglobin protein tetramers were analyzed using HPLC analysis following a protocol derived from Gravett et al. Science 2018. Briefly, approximately 1 million cells were lysed in 100 uL of water with 10 uL of lysate used per injection. Hemolysates were cleared by centrifugation and analyzed for identity and levels of hemoglobin variants (HbF and HbA) by cation-exchange HPLC with a weak cation-exchange column (Poly CAT A: 35 mm×4.6 mm, Poly LC, Inc., Columbia, MD). Hemoglobin isotype peaks were eluted with a linear gradient of phase B from 0% to 80% at A410 nm (Mobile Phase A: 20 mM Bis-Tris, 2 mM KCN, pH 6.95; Phase B:20 mM Bis-Tris, 2 mM KCN, 0.2 M sodium chloride, pH 6.55). Species were monitored with UV absorbance at 410 nm. Retention times for hemoglobin species was optimized using the hemoglobin FASC control (PerkinElmer) as isotype controls for HbF, HbA, HbS and HbC. The abundance of HbF, HbS, and HbA was quantified by calculating the area under the curve for each species in the samples. % HbF was calculated as HbF/(HbF+HbS+HbA)*100.

**[0230]** 100 nM of Compound 1 and 100 nM of Compound 2 decreased BCL11A and increase HBG1 and HBG2 expression in all donors studied (i.e., D069, D144, and D326 donors), as shown in FIG. **2**. It was observed that expression of the housekeeping gene TFRC did not result in substantial changes in expression upon exposure to Compound 1 or Compound 2. However, an approximately 2-fold increase in percentage HbF by HPLC at 100 nM Compound 1 or 100 nM Compound 2.

Example 3. Dependence of Compound 1 Concentration on BCL11A Expression, HBG1 Expression, HBG2 Expression, and Percentage HbF

**[0231]** A single donor (D069) was treated with Compound 1 to generate 4-point concentration response curves of fold changes in BCL11A expression, HBG1 expression, and HBG2 expression, and percentage HbF levels. Human Mobilized Peripheral Blood Primary CD34+ cells from 1 healthy donor were expanded from thaw by seeding 100,000 viable cells/mL in a culture flask containing CD34+ Phase 1 Media comprised of IMDM, 100 ng/ml hSCF, 5 ng/mL IL-3, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin. The cells were supplemented by adding an additional 1X culture volume of CD34+ Phase 1 Media on Day 3 after thaw. At Day 7 post-thaw, cells were seeded at 0.111×10^6 cells/ml in 1.5 mLs of Phase 1 media in 12-well plates and compound was applied. On Day 10 post-thaw, cells were differentiated towards the erythroid lineage by complete medium exchange into CD34+ Phase 2 Media comprised of IMDM, 100 ng/ml hSCF, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin and compound treatment was reapplied. On Day 12 post-thaw the plates were centrifuged, and 1 mL of Phase 2 media exchanged with fresh Phase 2 media and compound. The cells were harvested on Day 14 post-thaw for downstream analyses.

**[0232]** RNA was extracted from Day 14 post-thaw primary CD34+ cells that were differentiated and treated for 7 days with DMSO, 11 nM, 33 nM, 100 nM, or 300 nM of Compound 1 using Ambion mirVana RNA extraction kits. Purified RNA samples were submitted for library preparation and deep sequencing at Novogene. Sequenced raw reads of fastq files from all samples were mapped to hg38 genome assemblies using ArrayStudio aligner. Raw read counts and FPKM were calculated for all genes and DESeq2 was applied to calculate differentially expressed genes using general linear model. The statistical cutoff of absolute fold change greater than 4 (fdr<0.05, abs(FC)>4, log2(FPKM+1)>1).

**[0233]** Hemoglobin protein tetramers were analyzed using HPLC analysis following a protocol derived from Gravett et al. Science 2018. Briefly, approximately 1 million cells were lysed in 100 uL of water with 10 uL of lysate used per injection. Hemolysates were cleared by centrifugation and analyzed for identity and levels of hemoglobin variants (HbF and HbA) by cation-exchange HPLC with a weak cation-exchange column (Poly CAT A: 35 mm×4.6 mm, Poly LC, Inc., Columbia, MD). Hemoglobin isotype peaks were eluted with a linear gradient of phase B from 0% to 80% at A410 nm (Mobile Phase A: 20 mM Bis-Tris, 2 mM KCN, pH 6.95; Phase B:20 mM Bis-Tris, 2 mM KCN, 0.2 M sodium chloride, pH 6.55). Species were monitored with UV absorbance at 410 nm. Retention times for hemoglobin species was optimized using the hemoglobin FASC control (PerkinElmer) as isotype controls for HbF, HbA, HbS and HbC. The abundance of HbF, HbS, and HbA was quantified by calculating the area under the curve for each species in the samples. % HbF was calculated as HbF/(HbF+HbS+HbA)*100.

**[0234]** A decrease in BCL11A expression, an increase in HBG1 expression, an increase in HBG2 expression, and an increase in HbF protein levels were observed in a concentration-dependent fashion and at similar concentrations, as shown in FIG. **3**.

## Example 4. PRC2 Inhibition Reduces Expression of BCL11A Resulting in Induction of HBG1 Expression, Induction of HBG2 Expression, and Percentage HbF

**[0235]** The effect of PRC2 inhibition on BCL11A expression, HBGI expression, HBG2 expression, and percentage HbF in two different CD34+ donors was studied. Human Mobilized Peripheral Blood Primary CD34+ cells from 2 healthy donors were expanded from thaw by seeding 100,000 viable cells/mL in a culture flask containing CD34+ Phase 1 Media comprised of IMDM, 100 ng/mL hSCF, 5 ng/ml IL-3, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin. The cells were supplemented by adding an additional 1× culture volume of CD34+ Phase 1 Media on Day 3 after thaw. At Day 7 post-thaw, cells were seeded at 0.111×10^6 cells/ml in 1.5 mLs of Phase 1 media in 12-well plates and compound was applied. On Day 10 post-thaw, cells were differentiated towards the erythroid lineage by complete medium exchange into CD34+ Phase 2 Media comprised of IMDM, 100 ng/mL hSCF, 3 IU/mL EPO, 250 μg/mL transferrin, 2.5% normal human serum, 1% pen/strep, 10 ng/ml heparin, 10 μg/mL insulin and compound treatment was reapplied. On Day 12 post-thaw the plates were centrifuged, and 1 mL of Phase 2 media exchanged with fresh Phase 2 media and compound. The cells were harvested on Day 14 post-thaw for downstream analyses.

**[0236]** RNA was extracted from Day 14 post-thaw primary CD34+ cells that were differentiated and treated for 7 days with DMSO, Compound 1 (11 nM, 33 nM, 100 nM, 300 nM), Compound 2 (11 nM, 33 nM, 100 nM, 300 nM), Compund 3 (37 nM, 111 nM, 333 nM, 1 uM), Compound 4 (37 nM, 111 nM, 333 nM, 1 uM) using Ambion mirVana RNA extraction kits. Purified RNA samples were submitted for library preparation and deep sequencing at Novogene. Sequenced raw reads of fastq files from all samples were mapped to hg38 genome assemblies using ArrayStudio aligner. Raw read counts and FPKM were calculated for all genes and DESeq2 was applied to calculate differentially expressed genes using general linear model. The statistical cutoff of absolute fold change greater than 4 (fdr<0.05, abs(FC)>4, log2(FPKM+1)>1).

**[0237]** Hemoglobin protein tetramers were analyzed using HPLC analysis following a protocol derived from Gravett et al. Science 2018. Briefly, approximately 1 million cells were lysed in 100 uL of water with 10 uL of lysate used per injection. Hemolysates were cleared by centrifugation and analyzed for identity and levels of hemoglobin variants (HbF and HbA) by cation-exchange HPLC with a weak cation-exchange column (Poly CAT A: 35 mm×4.6 mm, Poly LC, Inc., Columbia, MD). Hemoglobin isotype peaks were eluted with a linear gradient of phase B from 0% to 80% at A410 nm (Mobile Phase A: 20 mM Bis-Tris, 2 mM KCN, pH 6.95; Phase B:20 mM Bis-Tris, 2 mM KCN, 0.2 M sodium chloride, pH 6.55). Species were monitored with UV absorbance at 410 nm. Retention times for hemoglobin species was optimized using the hemoglobin FASC control (PerkinElmer) as isotype controls for HbF, HbA, HbS and HbC. The abundance of HbF, HbS, and HbA was quantified by calculating the area under the curve for each species in the samples. % HbF was calculated as HbF/(HbF+HbS+HbA)*100.

**[0238]** From the procedure, aggregate data from two different CD34+ donors (D069 and D301) and multiple compounds that inhibit PRC2, particularly Compound 1, Compound 2, Compound 3, and Compound 4 were collected, as shown in FIG. **4**A, FIG. **4**B, and FIG. **4**C.

**[0239]** The data show that HBG1 mRNA expression level (FIG. **4**A), HBG2 mRNA expression level (FIG. **4**B), and percentage HbF protein (FIG. **4**C) correlate to a decrease in BCL11A mRNA levels regardless of donor, concentration, or PRC2 inhibitor selected.

## Example 5. Effect of Various PRC2 Inhibitors on BCL11A, HBG1, and HBG2 Expression

**[0240]** 4-point concentration response curves of the PRC2 inhibitors Compound 1, Compound 2, Compound 3, and Compound 4 on BCL11A expression (FIG. **5**A), HBG1 expression (FIG. **5**B), and HBG2 expression (FIG. **5**C), were generated. The data show that all PRC2 inhibitors profiled show a reduction in BCL11A expression and a concomitant induction of HBG1 and HBG2 expression.

## Example 6. Studies of Effects of Compound 1 and Gene Knockdown BCL11A mRNA Levels

**[0241]** Whole blood of wildtype CD-1 mice were treated for 5 days with 10 mg/kg Compound 1, and which was maintained over time in the Townes sickle cell disease (SCD) mouse model (FIG. **6**). Furthermore, CRISPR-Cas9 in CD34+ cells was used to understand if loss-of-function of EED or BCL11A recapitulated the pharmacologic impact on fetal hemoglobin expression with Compound 1. Knockdown in vitro of both BCL11A and EED genes showed a significant reduction in BCL11A mRNA levels with a corresponding induction of HbF protein (FIG. **7**).

Whole Blood Real-Time Quantitative PCR (qRT-PCR)

**[0242]** Whole blood was collected and preserved in DNA/RNA Shield Solution. RNA was extracted with MagMAX mirVana Total RNA Isolation Kit with KingFisher™ Flex Purification System. 10 ng of RNA was used for one-step TaqMan RNA-to-Ct reaction using Taqman reverse transcriptase Multiplex Master Mix (ThermoFisher, #4484262) following the manufacturer's recommendations. Amplification was detected in a Quantstudio 7 Flex instrument from ThermoFisher. Transcript specific Taqman probes purchased from ThermoFisher are shown in Table 1. The relative

expression levels from each gene target were calculated and normalized to geometric mean of three reference genes (Gapdh, Oazl and Tfrc) using $2^{-4Ct}$ method.

Example 7. Comparative Studies of Compound 1 and Hydroxyurea (HU) in an SCD Mouse Model

**[0243]** The Townes SCD mouse model was used to study the in vivo pharmacologic activity of Compound 1 in a model with the relevant human globin genes (HBG1 and $HBB_{E6V}$) integrated into the mouse beta globin locus. Hydroxyurea was used as a benchmark for this 21-day study. The Compound 1 treatment was well-tolerated in the SCD mice and target engagement analysis found that levels of H3K27me3 were significantly reduced in Ter119+ bone marrow cells with Compound 1 treatment but not hydroxyurea treatment after 28 days of treatment as expected (FIG. **8**A). Compound 1 treatment led to increases in % F-cells when measured at Day 13 and Day 21, while hydroxyurea did not significantly impact F-cells (FIG. **8**B). Despite the Townes SCD mouse having low basal HbF expression, % HbF of total hemoglobin was quantified by HPLC and showed significant induction of HbF with Compound 1 treatment consistent with the 2-3 fold induction observed preclinically, while no change in HbF was observed with hydroxyurea (FIG. **8**C). The Compound 1 treated Townes mice showed a statistically significant reduction in spleen weight as a percent of total body weight by Day 21, further demonstrating the benefit of increased HbF on SCD-related symptomatology (FIG. **8**D). People living with sickle cell present with impaired erythropoiesis leading to elevated reticulocytes, decreased red blood cell count, and total hemoglobin, and additionally display markers of inflammation such as elevated neutrophils and white blood cells. Similarly, the Townes mouse model recapitulates these hematological aspects of SCD. The Compound 1 induced increase in HbF, although expressed at low levels relative to total hemoglobin, translated to positive improvements in hematological parameters in the Townes mice such as RBC count, total Hb, % reticulocytes, WBCs, and neutrophils (FIG. **8**E).

Equivalents

**[0244]** Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

**1**. A method of downregulating BCL11A in a cell comprising: contacting the cell sample with an EED, EHZ2, and/or PRC2 inhibitor in amount sufficient to decrease expression of BCL11A.

**2**. The method of claim **1**, wherein the cell is an erythroid cell differentiated from a CD34+ cell.

**3**. The method of claim **2**, wherein upon contacting the cell, HBG1 and/or HBG2 expression increases.

**4**. The method of any one of claims **1-3**, wherein upon contacting the cell with the protein inhibitor, the cell does or does not express fetal hemoglobin.

**5**. A method of identifying a patient having a BCL11A mediated disorder who may benefit from treatment comprising one or more inhibitors of EED, EHZ2, and/or PRC2, comprising determining an expression level of BCL11A in a sample obtained from the patient, wherein an increased expression level of BCL11A in the sample as compared to a reference expression level identifies the patient as one who may benefit from the EED, EHZ2, and/or PRC2 inhibitor treatment.

**6**. A method of treating a patient having a BCL11A mediated disorder, comprising administering to the patient a therapeutically effective amount of a EED, EHZ2, and/or PRC2 inhibitor, wherein the expression level of BCL11A in a sample obtained from the patient has been determined to be decreased after the administration as compared to a reference expression level.

**7**. The method of any one of claims **1-6**, wherein the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of an antibody against EED, EHZ2, and/or PRC2 or an antigen-binding fragment thereof, a small molecule, and a nucleic acid.

**8**. The method of claim **7**, wherein the nucleic acid is a EED, EHZ2, and/or PRC2-specific RNA interference agent, a vector encoding a RNA interference agent, or an aptamer that binds EED, EZH2, and/or PRC2.

**9**. The method of any one of claims **5-8**, wherein the BCL11A mediated disorder is selected from the group consisting of triple negative breast cancer, non-small cell lung cancer, glioblastoma, neuroblastoma, prostate cancer, type 2 diabetes, laryngeal squamous cell carcinoma, and Williams syndrome.

**10**. A method of treatment of a hemoglobinopathy in a subject comprising administering an effective amount of a composition comprising an inhibitor of EED, EHZ2, and/or PRC2, wherein the inhibitor of PRC2 downregulates the expression of BCL11A and whereby fetal hemoglobin expression is increased in the subject relative to prior to the administration.

**11**. The method of claim **10**, wherein the hemoglobinopathy is selected from the group consisting of sickle cell disease (SCD), α-thalassemia, and β-thalassemia.

**12**. The method of claim **11**, wherein the β-thalassemia is selected from the group consisting of sickle β-thalassemia, hemoglobin C β-thalassemia, and hemoglobin E β-thalassemia.

**13**. The method of claim **12**, wherein sickle β-thalassemia is selected from sickle β0 thalassemia and sickle β+thalassemia.

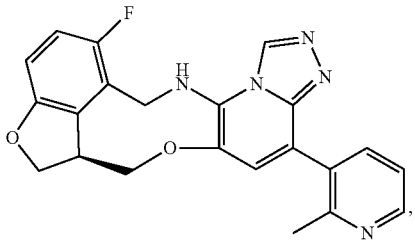
**14**. The method of any one of claims **1-13**, wherein the expression level of BCL11A is decreased by at least 25% relative to a reference level.

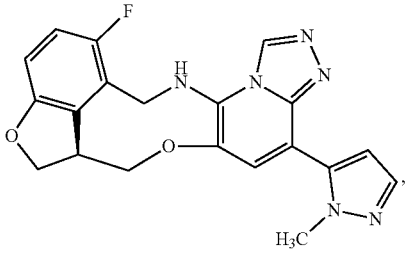
**15**. The method of any one of claims **1-14**, wherein the expression level is a protein expression level or a mRNA expression level.

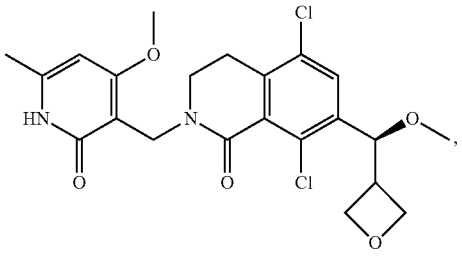
**16**. The method of claim **15**, wherein the mRNA expression level is determined by qPCR or RNA-Seq.

**17**. The method of claim **15**, wherein the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

**18**. The method of any one of claims **1-17**, wherein the EED, EHZ2, and/or PRC2 inhibitor is selected from the group consisting of:







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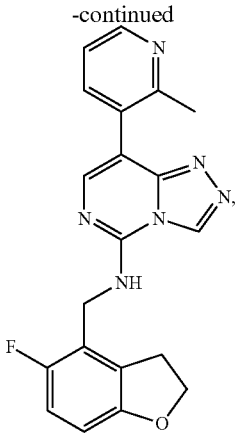

tazemetostat, CPI-0209, CPI-1205, EBI-2554, HH-2853, MAK-683, SHR-2554, valemetostat, PF-06821497, ORIC-944, and GSK-2816126.

**19**. A genetically modified cell comprising an insertion and/or deletion in a gene loci that encodes a protein selected from the group consisting of EED, EHZ2, and PRC2, wherein the insertion and/or deletion is capable of down-regulating expression of BCL11A in the cell.

**20**. The genetically modified cell of claim **19**, wherein the expression level of BCL11A is decreased by at least 25% relative to a reference level.

**21**. The genetically modified cell of claim **19** or **20**, wherein the expression level is a protein expression level or a mRNA expression level.

**22**. The genetically modified cell of claim **21**, wherein the mRNA expression level is determined by qPCR or RNA-Seq.

**23**. The genetically modified cell of claim **21**, wherein the protein expression level is determined using a method selected from the group consisting of high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), immunofluorescence, mass spectrometry, flow cytometry, and Western blot.

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