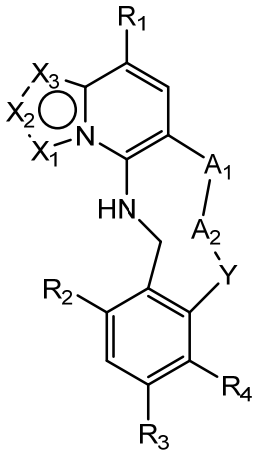
hepatocellular carcinoma, breast cancer, prostate cancer, etc. Activating mutations in EZH2 have been found in FL (follicular lymphoma) and DLBCL (diffuse large B cell lymphoma) patients. EED normally mediates repression of gene activity by binding to di- and trimethylated lysine 27 of histone 3 where 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.

[0005] 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. The need exists for small molecules that modulate EED and/or PRC2.

Summary

[0005b] In one aspect of the present disclosure, there is provided a compound of Formula I:



(I),

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

wherein:

X_1, X_2, and X_3 are independently is 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;

A_1 is a bond, –C(R_8)(R_9)–, –O–, –NR_8, –S–, –S(O)–, or –SO_2–;

A_2 and Y are independently at each occurrence –C(R_8)(R_9)–, –O–, –NR_8, –S–, –S(O)–, or –SO_2–;

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_5-C_8 cycloalkenyl, C_3-C_8 spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_6;

R_2 and R_3 are 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, wherein the alkyl, alkoxy, alkenyl, or alkynyl is optionally substituted with one or more R_7;

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,

or R_4 and R_9 when taken together can form C_3-C_{10} cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

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, -$S(O)_2R_8$, –N$R_8$$S(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, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7;

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, -$S(O)_2R_8$, –N$R_8$$S(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

two R_6 can combine to form C_3-C_{10} cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

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;

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};

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};

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

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; and

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.

[0005c] In another aspect of the present disclosure, there is provided A pharmaceutical composition comprising, a compound of any one of claims 1-31, and a pharmaceutically acceptable carrier.

[0005d] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder associated with modulation of Embryonic Ectoderm Development (EED).

[0005e] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder associated with modulation of Polycomb Repressive Complex 2 (PRC2).

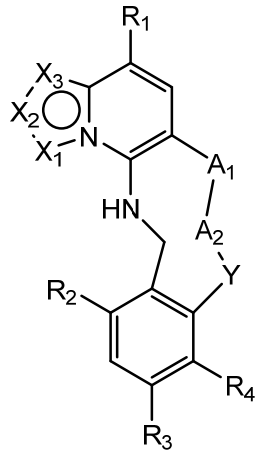
[0005f] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating thoracic aortic aneurysm, coronary heart disease, stenotic disease, pulmonary artery hypertension (PAH), liver fibrosis, allergic inflammation, retinitis pigmentosa, septic shock, herpes simplex virus, human cytomegalovirus, α-thalassemia, familial atrial fibrillation, common variable immunodeficiency, aneurysm-osteoarthritis syndrome, and acquired immunodeficiency syndrome.

[0005g] In another aspect of the present disclosure, there is provided a compound disclosed herein, for use in treating a disease or disorder associated with the modulation of Embryonic Ectoderm Development (EED).

[0005h] In a further aspect of the present disclosure, there is provided a compound disclosed herein, for use in treating a disease or disorder associated with the modulation of Polycomb Repressive Complex 2 (PRC2).

[0005i] In another aspect of the present disclosure, there is provided a compound disclosed herein or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, for use in treating thoracic aortic aneurysm, coronary heart disease, stenotic disease, pulmonary artery hypertension (PAH), liver fibrosis, allergic inflammation, retinitis pigmentosa, septic shock, herpes simplex virus, human cytomegalovirus, α-thalassemia, familial atrial fibrillation, common variable immunodeficiency, aneurysm-osteoarthritis syndrome, and acquired immunodeficiency syndrome.

[0006] A first example of the present disclosure relates to compounds of Formula I:



(I),

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

wherein:

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;

A_1 is a bond, $–C(R_8)(R_9)–$, –O–, $–NR_8$, –S–, –S(O)–, or $–SO_2–$;

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;

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};

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};

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

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; and

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.

[0007] Another example of the present disclosure relates to a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may further include an excipient, diluent, or surfactant.

[0008] Another example of the present disclosure is directed to a method of treating a disease or disorder associated with modulation of embryonic ectoderm development (EED). The method involves administering to a patient in need thereof an effective amount of the compound of Formula I.

[0009] Another example of the present disclosure relates to a method of treating a disease or disorder associated with modulation of Polycomb Repressive Complex 2 (PRC2). The method comprises administering to a patient in need thereof an effective amount of the compound of Formula I.

[0010] The present disclosure further provides methods of treating a cancer selected from diffused large B cell lymphoma, follicular lymphoma, other lymphomas, leukemia, multiple myeloma, mesothelioma, gastric cancer, malignant rhabdoid tumor, hepatocellular carcinoma,

prostate cancer, breast carcinoma, bile duct and gallbladder cancers, bladder carcinoma, brain tumors including neuroblastoma, schwannoma, glioma, glioblastoma and astrocytoma, cervical cancer, colon cancer, melanoma, endometrial cancer, esophageal cancer, head and neck cancer, lung cancer, nasopharyngeal carcinoma, ovarian cancer, pancreatic cancer, renal cell carcinoma, rectal cancer, thyroid cancers, parathyroid tumors, uterine tumors, and soft tissue sarcomas.

[0011] The present disclosure further provides methods of a blood disorder selected from Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML) (e.g., acute promyelocytic leukemia, APL), Amyloidosis, Anemia, Aplastic anemia, Bone marrow failure syndromes, Chronic lymphocytic leukemia (CLL), Chronic myeloid leukemia (CML), Deep vein thrombosis (DVT), Diamond-Blackfan anemia, Dyskeratosis congenita (DKC), Eosinophilic disorder, Essential thrombocythemia, Fanconi anemia, Gaucher disease, Hemochromatosis, Hemolytic anemia, Hemophilia, Hereditary spherocytosis, Hodgkin's lymphoma, Idiopathic thrombocytopenic purpura (ITP), Inherited bone marrow failure syndromes, Iron-deficiency anemia, Langerhans cell histiocytosis, Large granular lymphocytic (LGL) leukemia, Leukemia, Leukopenia, Mastocytosis, Monoclonal gammopathy, Multiple myeloma, Myelodysplastic syndromes (MDS), Myelofibrosis, Myeloproliferative neoplasms (MPN), Non-Hodgkin's lymphoma, Paroxysmal nocturnal hemoglobinuria (PNH), Pernicious anemia (B12 deficiency), Polycythemia vera, Porphyria, Post-transplant lymphoproliferative disorder (PTLD), Pulmonary embolism (PE), Shwachman-Diamond syndrome (SDS), sickle cell disease (SCD), Thalassemia (e.g., β-thalassemia), Thrombocytopenia, Thrombotic thrombocytopenic purpura (TTP), Venous thromboembolism, Von Willebrand disease, and Waldenstrom's macroglobulinemia (lymphoplasmacytic lymphoma).

[0012] The present disclosure further provides methods of treating sickle cell disease (SCD) or β-thalassemia. The method comprises administering to a patient in need thereof an effective amount of the compound of Formula I.

[0013] The present disclosure further provides methods of treating thoracic aortic aneurysm, coronary heart disease, stenotic disease, pulmonary artery hypertension (PAH), liver fibrosis, allergic inflammation, retinitis pigmentosa, septic shock, herpes simplex virus, human cytomegalovirus, α-thalassemia, familial atrial fibrillation, common variable immunodeficiency, aneurysm-osteoarthritis syndrome, and acquired immunodeficiency syndrome. The method

comprises administering to a patient in need thereof an effective amount of the compound of Formula I.

[0014] The present disclosure further provides use of a compound of Formula I for treating a disease or disorder associated with the modulation of embryonic ectoderm development (EED).

[0015] The present disclosure further provides use of a compound of Formula I for treating a disease or disorder associated with the modulation of Polycomb Repressive Complex 2 (PRC2).

[0016] The present disclosure further provides a compound of Formula I for use in the manufacture of a medicament for treating a disorder or disease associated with embryonic ectoderm development (EED).

[0017] The present disclosure further provides a compound of Formula I for use in the manufacture of a medicament for treating a disorder or disease associated with Polycomb Repressive Complex 2 (PRC2).

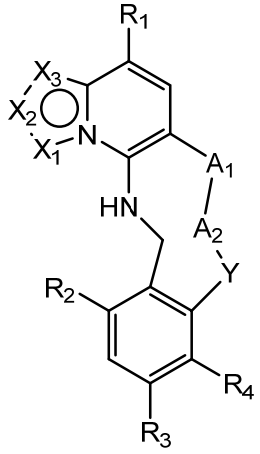
Detailed Description of the Invention

[0018] EED mediates repression of gene activity by binding to di- and trimethylated lysine 27 of histone 3 where it allosterically activates the methyltransferase activity of PRC2, functions to recruit PRC1 to H3K27me3 loci, enhances PRC1 mediated H2A ubiquitin E3 ligase activity and regulates PRC2 in the silencing of expression of genes and gene clusters involved in development, *i.e.*, Hox genes, and in X chromosome inactivation. Thus, EED and/or PRC2 provides a pharmacological target for the diseases or disorders, including cancers, to impact transcription.

[0019] Hemoglobin is the critical protein involved in oxygen transport throughout the body of vertebrates. It is found in red blood cells and consists of two α subunits and two β subunits. The composition of hemoglobin is developmentally regulated where the human genome encodes multiple versions of these proteins that are expressed during distinct stages of development (Blobel *et al.*, Exp. Hematol. 2015, incorporated herein by reference; Stamatoyannopoulos G, Exp. Hematol. 2005, incorporated herein by reference). In general, fetal hemoglobin (HbF) is composed of two subunits of hemoglobin γ (HBγ) and two subunits of hemoglobin α (HBα) and adult hemoglobin (HbA) is composed of two subunits of hemoglobin β (HBβ) and two subunits of HBα. Thus, the β subunit utilized during the fetal stage of development is (HBγ) and switches to hemoglobin β (HBβ) after birth. Red blood cell disorders like sickle cell disease (SCD) and

What is claimed is:

1. A compound of Formula I:



(I),

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

wherein:

X_1, X_2, and X_3 are independently is 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;

A_1 is a bond, $–C(R_8)(R_9)–$, –O–, $–NR_8$, –S–, –S(O)–, or $–SO_2–$;

A_2 and Y are independently at each occurrence $–C(R_8)(R_9)–$, –O–, $–NR_8$, –S–, –S(O)–, or $–SO_2–$;

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_5-C_8 cycloalkenyl, C_3-C_8 spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, spirocycloalkyl, spiroheterocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_6;

R_2 and R_3 are 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, wherein the alkyl, alkoxy, alkenyl, or alkynyl is optionally substituted with one or more R_7;

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,

or R_4 and R_9 when taken together can form C_3-C_{10} cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

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, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7;

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

two R_6 can combine to form C_3-C_{10} cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

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;

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};

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};

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

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; and

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.

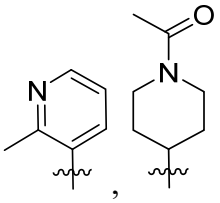
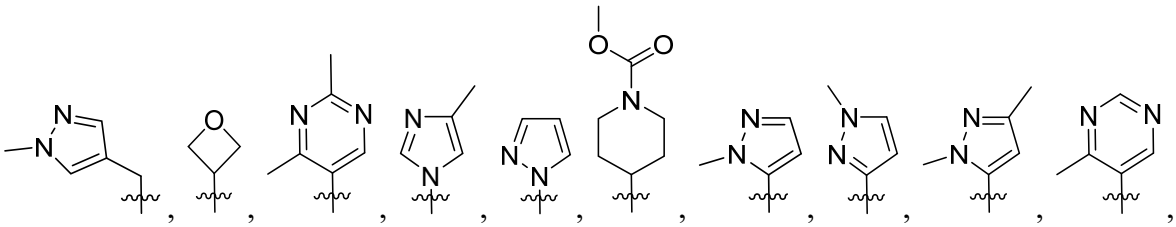
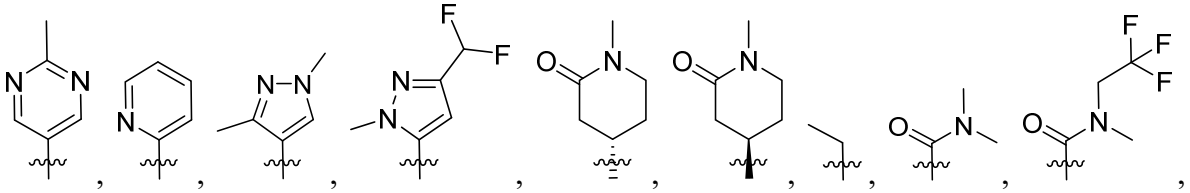
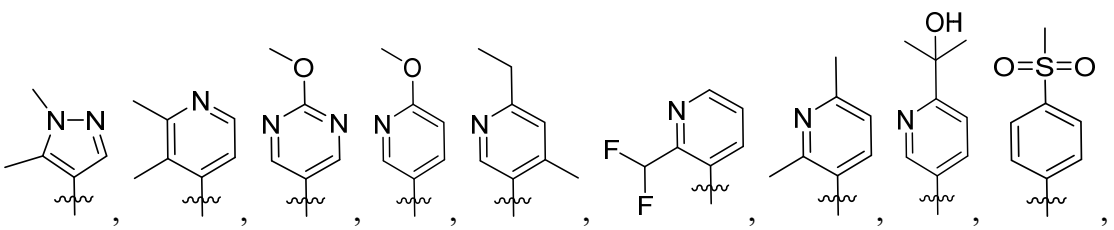
2. The compound of claim 1, wherein X_1, X_2, or X_3 is N.

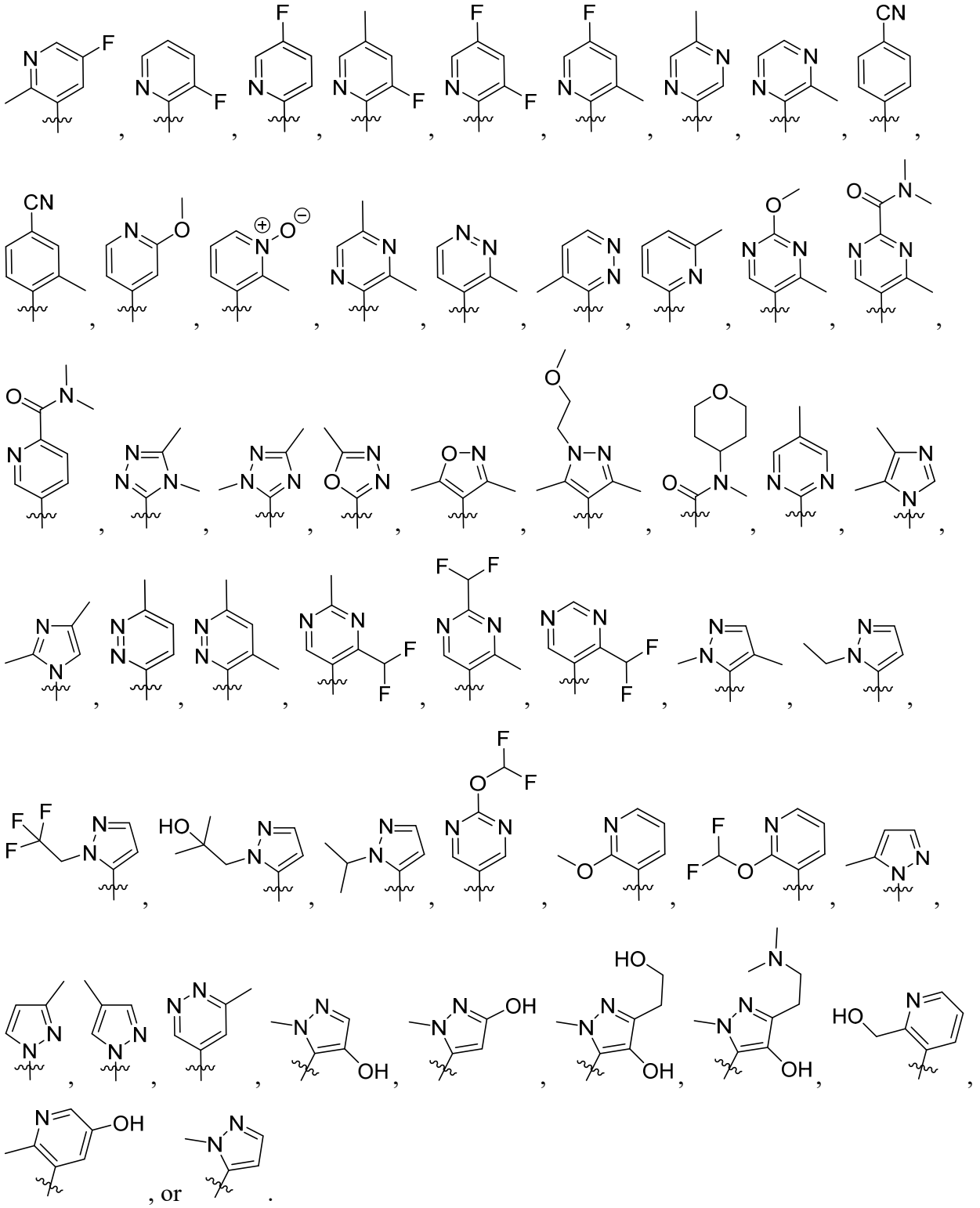
3. The compound of claim 1, wherein X_1, X_2, or X_3 is $C(R_5)$.

4. The compound of any one of claims 1-3, wherein R_1 is heteroaryl.

5. The compound of any one of claims 1-3, wherein R_1 is heterocyclyl.

6. The compound of any one of claims 1-3, wherein R_1 is H, $–C(O)NR_8R_9$, or C_1-C_6 alkyl.

7. The compound of any one of claims 1-3, wherein R_1 is selected from: , , , ,



8. The compound of any one of claims 1-7, wherein R_2 is H, C_1-C_6 alkyl, or halogen.

9. The compound of any one of claims 1-8, wherein A_1 is –O– or –C(R_8)(R_9)–.

10. The compound of any one of claims 1-9, wherein A_2 is –O– or –C(R_8)(R_9)–.

11. The compound of any one of claims 1-10, wherein Y is –C(R_8)(R_9)– or –NR_8R_9.

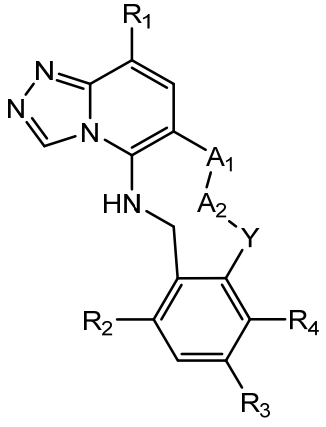
12. The compound of any one of claims 1-11, wherein R_4 and R_9 can form C_3-C_{10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

13. The compound of any one of claims 1-12, wherein R_3 is H, OH, or halogen.

14. The compound of any one of claims 1-12, wherein R_3 is C_1-C_6 alkyl.

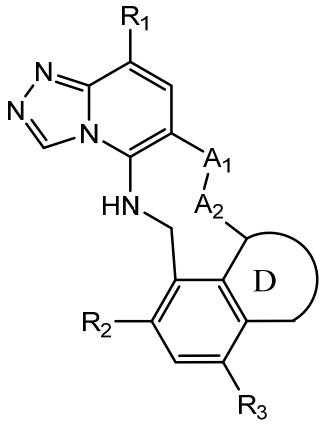
15. The compound of any one of claims 1-14, wherein R_4 is C_1-C_6 alkyl optionally substituted with one or more R_7.

16. The compound of claim 1 having the formula Ia:



(Ia).

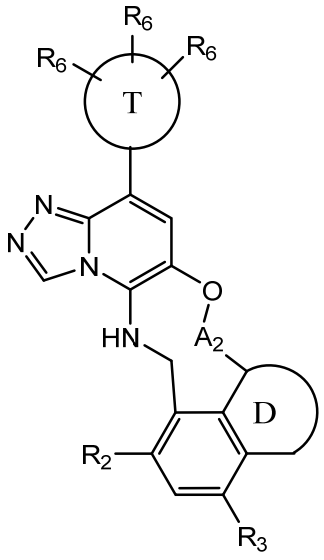
17. The compound of claim 1 having the formula Ib:



(Ib)

wherein the D ring represents a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl .

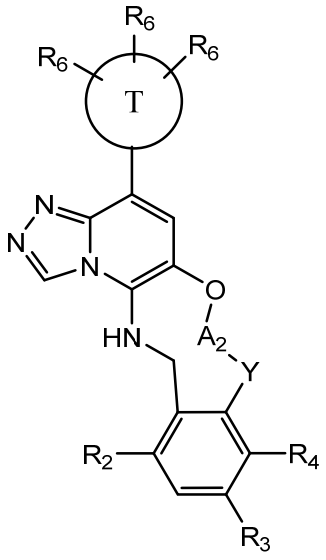
18. The compound of claim 1 having the formula Ic:



(Ic),

wherein the D and T rings independently represent a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

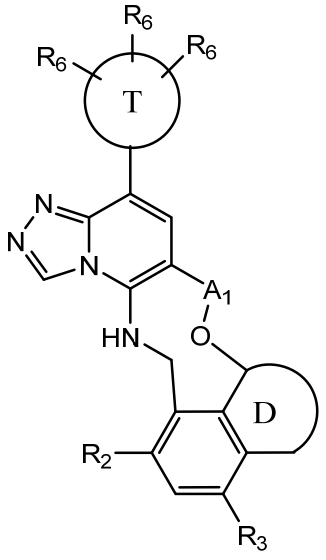
19. The compound of claim 1 having the formula Id:



(Id),

wherein the T ring represents a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

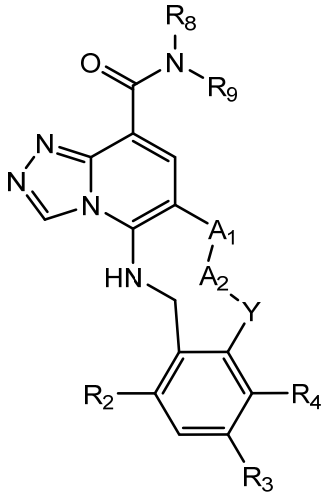
20. The compound of claim 1 having the formula If;



(If)

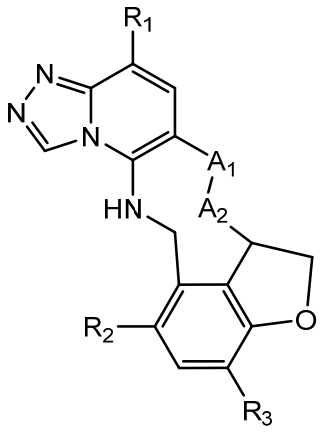
wherein the D and T rings independently represent a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

21. The compound of claim 1 having the formula Ig:



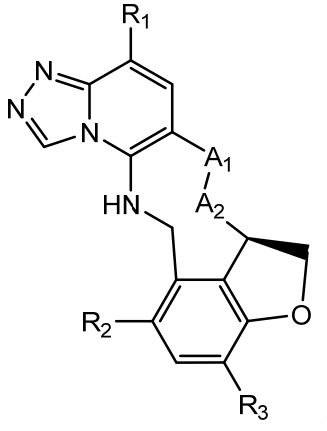
(Ig).

22. The compound of claim 1 having the formula Ii:



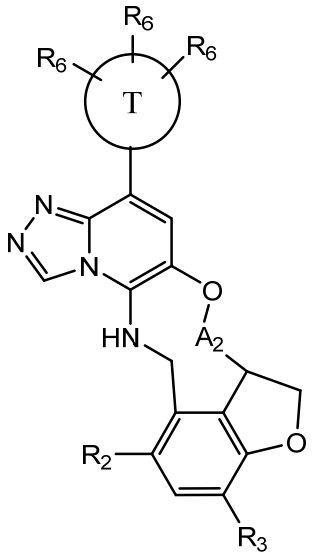
(Ih).

23. The compound of claim 1 having the formula Ii-a:



(Ih-a).

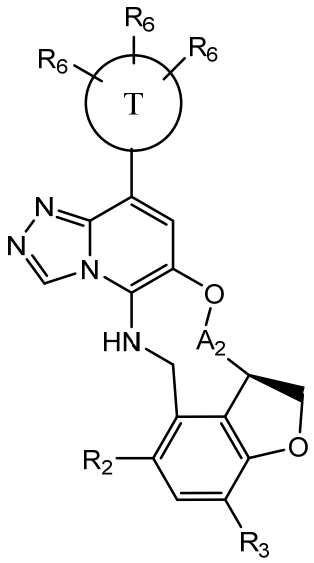
24. The compound of claim 1 having the formula Ii:



(Ii)

wherein the T ring represents a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

25. The compound of claim 1 having the formula Ii-a:

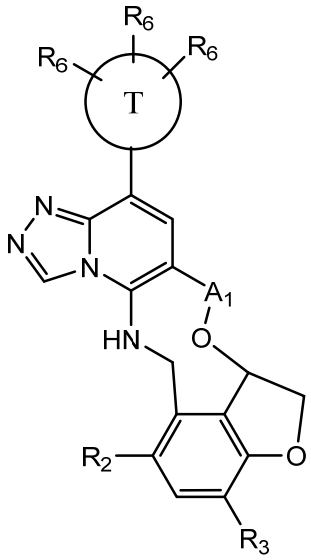


(Ii-a)

wherein the T ring represents a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

26. The compound of any one of claims 24-25, wherein the T ring represents a heterocyclyl.

27. The compound of claim 1 having the formula Ij:

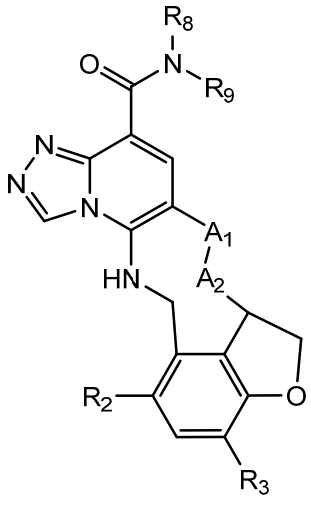


(Ij)

wherein the T ring represents a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl.

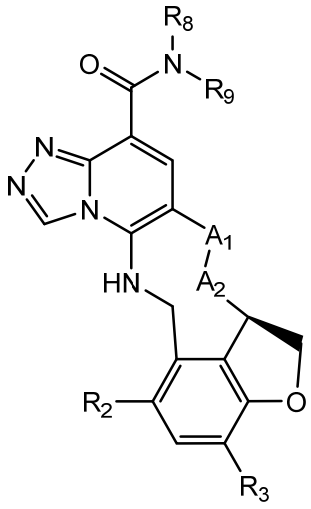
28. The compound of claim 27, wherein the T ring represents a heterocyclyl.

29. The compound of claim 1 having the formula Ik:



(Ik).

30. The compound of claim 1 having the formula Ik-a:



(Ik-a).

31. The compound of claim 1 selected from the group consisting of:

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
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
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
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[1',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
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
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[1',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[1',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[1',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[1',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[1',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
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

.

32. A pharmaceutical composition comprising, a compound of any one of claims 1-31, and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32 further comprising at least one additional therapeutic agent.

34. The pharmaceutical composition of claim 33, wherein the additional therapeutic agent is selected from anti-cancer agents, immunomodulators, anti-allergic agents, anti-emetics, pain relievers, cytoprotective agents, anti-sickling agents, or combinations thereof.

35. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is an EZH2 inhibitor.

36. The pharmaceutical composition of claim 38, wherein the additional therapeutic agent is selected from N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-

pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide (tazemetostat), (2R)-7-chloro-2-[4-(dimethylamino)cyclohexyl]-N-[(4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-2,4-dimethyl-1,3-benzodioxole-5-carboxamide (valemetostat, DS-3201b), N-[(4-methoxy-6-methyl-2-oxo-1H-pyridin-3-yl)methyl]-2-methyl-1-[(1R)-1-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]ethyl]indole-3-carboxamide (CPI-1205), (S)-1-(sec-butyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-methyl-6-(6-(piperazin-1-yl)pyridin-3-yl)-1H-indole-4-carboxamide (GSK2816126), (R)-5,8-dichloro-7-(methoxy(oxetan-3-yl)methyl)-2-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (PF-06821497), SHR2554, or combinations thereof.

37. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is hydroxyurea.

38. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is selected from 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (voxelotor, GBT-440), P-Selectin antibodies, L-Glutamine, or combinations thereof.

39. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is selected from anti-adhesion agents.

40. The pharmaceutical composition of claim 39, wherein the additional therapeutic agent is selected from crizanlizumab (SEG101), (2S)-2-[(2R,3R,4S,5S,6R)-3-benzoyloxy-2-[(1R,2R,3S,5R)-3-[(2,4-dioxo-1H-pyrimidine-6-carbonyl)amino]-5-[2-[[2-[2-[2-oxo-2-[(3,6,8-trisulfonaphthalen-1-yl)amino]ethoxy]ethoxy]acetyl]amino]ethylcarbamoyl]-2-[(2S,3S,4R,5S,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxycyclohexyl]oxy-5-hydroxy-6-(hydroxymethyl)oxan-4-yl]oxy-3-cyclohexylpropanoic acid (rivipansel, GMI-1070), sevuparin, 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(oxan-4-yl)-5H-pyrazolo[3,4-d]pyrimidin-4-one (PF-04447943), inclacumab (LC1004-002), 3-[3-[4-(1-aminocyclobutyl)phenyl]-5-phenylimidazo[4,5-b]pyridin-2-yl]pyridin-2-amine (miransertib, ARQ 092), or combinations thereof.

41. The pharmaceutical composition of claim 33-34, wherein the additional therapeutic agent is selected from anti-sickling agents.

42. The pharmaceutical composition of claim 41, wherein the additional therapeutic agent is selected from 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (voxelotor, GBT-440), 6-[(3S,4S)-4-Methyl-1-(2-pyrimidinylmethyl)-3-pyrrolidinyl]-3-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7H)-one (IMR-687), or combinations thereof.

43. The pharmaceutical composition of claim 33-34, wherein the additional therapeutic agent is selected from detoxification agents.

44. The pharmaceutical composition of claim 43, wherein the additional therapeutic agent is LJPC-401.

45. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is selected from anti-inflammatory agents, anti-thrombiotic agents, or combinations thereof.

46. The pharmaceutical composition of claim 45, wherein the additional therapeutic agent is selected from (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (brilinta, tricagrelor), (2R)-3,3,3-trifluoro-2-[[[5-fluoro-2-[1-[(2-fluorophenyl)methyl]-5-(1,2-oxazol-3-yl)pyrazol-3-yl]pyrimidin-4-yl]amino]methyl]-2-hydroxypropanamide (olinciguat), NKTT120, or combinations thereof.

47. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is sanguinate.

48. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent causes disruption of PRC2.

49. The pharmaceutical composition of claims 33-34, wherein the additional therapeutic agent is AZD9291.

50. Use of a compound of any one of claims 1-31 or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder associated with modulation of Embryonic Ectoderm Development (EED).

51. Use of a compound of any one of claims 1-31 or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating a disease or disorder associated with modulation of Polycomb Repressive Complex 2 (PRC2).

52. The use of claim 50 or 51, wherein the disease or disorder is a blood disorder.

53. The use of claim 52, wherein the blood disorder is selected from Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Amyloidosis, Anemia, Aplastic anemia, Bone marrow failure syndromes, Chronic lymphocytic leukemia (CLL), Chronic myeloid leukemia (CML), Deep vein thrombosis (DVT), Diamond-Blackfan anemia, Diffused large B cell lymphoma, Dyskeratosis congenita (DKC), Eosinophilic disorder, Essential thrombocythemia, Fanconi anemia, Follicular lymphoma, Gaucher disease, Hemochromatosis, Hemolytic anemia, Hemophilia, Hereditary spherocytosis, Hodgkin's lymphoma, Idiopathic thrombocytopenic purpura (ITP), Inherited bone marrow failure syndromes, Iron-deficiency anemia, Langerhans cell histiocytosis, Large granular lymphocytic (LGL) leukemia, Leukemia, Leukopenia, Mastocytosis, Monoclonal gammopathy, Multiple myeloma, Myelodysplastic syndromes (MDS), Myelofibrosis, Myeloproliferative neoplasms (MPN), Non-Hodgkin's lymphoma, Paroxysmal nocturnal hemoglobinuria (PNH), Pernicious anemia (B12 deficiency), Polycythemia vera, Porphyria, Post-transplant lymphoproliferative disorder (PTLD), Pulmonary embolism (PE), Shwachman-Diamond syndrome (SDS), sickle cell disease (SCD), β-thalassemia, Thrombocytopenia, Thrombotic thrombocytopenic purpura (TTP), Venous

thromboembolism, Von Willebrand disease, and Waldenstrom's macroglobulinemia (lymphoplasmacytic lymphoma).

54. The use of claim 52 or 53, wherein the blood disorder is sickle cell disease (SCD).

55. The use of claim 52 or 53, wherein the blood disorder is β-thalassemia.

56. The use of claim 50 or 51, wherein the disease or disorder is cancer.

57. The use of claim 56, wherein the cancer is selected from Mesothelioma, Gastric cancer, Malignant rhabdoid tumor, Hepatocellular carcinoma, Prostate cancer, Breast carcinoma, Bile duct and Gallbladder cancers, Bladder carcinoma, Brain tumors including Neuroblastoma, Schwannoma, Glioma, Glioblastoma and Astrocytoma, Cervical cancer, Colon cancer, Melanoma, Endometrial cancer, Esophageal cancer, Head and neck cancer, Lung cancer, Nasopharyngeal carcinoma, Ovarian cancer, Pancreatic cancer, Renal cell carcinoma, Rectal cancer, Thyroid cancers, Parathyroid tumors, Uterine tumors, and Soft tissue sarcomas.

58. Use of a compound of any one of claims 1-31 or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, in the manufacture of a medicament for treating thoracic aortic aneurysm, coronary heart disease, stenotic disease, pulmonary artery hypertension (PAH), liver fibrosis, allergic inflammation, retinitis pigmentosa, septic shock, herpes simplex virus, human cytomegalovirus, α-thalassemia, familial atrial fibrillation, common variable immunodeficiency, aneurysm-osteoarthritis syndrome, and acquired immunodeficiency syndrome.

59. A compound of any one of claims 1-31, for use in treating a disease or disorder associated with the modulation of Embryonic Ectoderm Development (EED).

60. A compound of any one of claims 1-31, for use in treating a disease or disorder associated with the modulation of Polycomb Repressive Complex 2 (PRC2).

61. A compound of any one of claims 1-31 or the pharmaceutically acceptable salt, prodrug, solvate, hydrate, enantiomer, isomer, or tautomer thereof, for use in treating thoracic aortic aneurysm, coronary heart disease, stenotic disease, pulmonary artery hypertension (PAH), liver fibrosis, allergic inflammation, retinitis pigmentosa, septic shock, herpes simplex virus, human cytomegalovirus, α-thalassemia, familial atrial fibrillation, common variable immunodeficiency, aneurysm-osteoarthritis syndrome, and acquired immunodeficiency syndrome.