Title: NOVEL SUBSTITUTED BICYCLIC COMPOUNDS AS BROMODOMAIN INHIBITORS

Abstract: The invention relates to substituted bicyclic compounds, which are useful for inhibition of BET protein function by binding to bromodomains, pharmaceutical compositions comprising these compounds, and use of the compounds and compositions in therapy.
Novel Substituted Bicyclic Compounds as Bromodomain inhibitors

[001] This application claims priority from U.S. Provisional Patent Application No. 61/837,830, filed June 21, 2013, and U.S. Provisional Patent Application No. 61/911,668, filed December 4, 2013, both which are hereby incorporated by reference in their entirety.


[003] Interfering with BET protein interactions via bromodomain inhibition results in modulation of transcriptional programs that are often associated with diseases characterized by dysregulation of cell cycle control, inflammatory cytokine expression, viral transcription, hematopoietic differentiation, insulin transcription, and adipogenesis. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," *Nat Rev Cancer* 12(7):465-77 (2012). BET inhibitors are believed to be useful in the treatment of diseases or conditions related to systemic or tissue inflammation, inflammatory responses to infection or hypoxia, cellular activation and proliferation, lipid metabolism, fibrosis, and the prevention and treatment of viral infections.


BET inhibitors may be useful in the treatment of a variety of chronic autoimmune inflammatory conditions. Thus, one aspect of the invention provides compounds, compositions, and methods for treating autoimmune and/or inflammatory diseases by administering one or more compounds of the invention or pharmaceutical compositions comprising one or more of those compounds. Examples of autoimmune and inflammatory diseases, disorders, and syndromes that may be treated using the compounds and methods of the invention include but are not limited to, inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis (Zhang, G., et al., "Down-regulation of NF-kappaB Transcriptional Activity in HIV-associated Kidney Disease by BRD4 Inhibition," J Biol Chem, 287(34):SS40-51 (2012)), osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis (Prinjha, R.K., J. VVitherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains" Trends Pharmacol Sci 33(3): 146-53 (2012)), Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia,

[007] BET inhibitors may be useful in the treatment of a wide variety of acute inflammatory conditions. Thus, one aspect of the invention provides compounds, compositions, and methods for treating inflammatory conditions including but not limited to, acute gout, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement, such as glomerulonephritis, vasculitis, including giant cell arteritis, Wegener's granulomatosis, polyarteritis nodosa, Behcet's disease, Kawasaki disease, and Takayasu's arteritis.

[008] BET inhibitors may be useful in the prevention and treatment of diseases or conditions that involve inflammatory responses to infections with bacteria, viruses, fungi, parasites, and their toxins, such as, but not limited to sepsis, sepsis syndrome, septic shock (Nicodeme, E., et al., "Suppression of inflammation by a synthetic histone mimic," *Nature* 468(7327):1119-23 (2010)), systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, adult respiratory distress syndrome (ARDS), acute renal failure, fulminant hepatitis, burns, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria, and SIRS associated with viral infections, such as influenza, herpes zoster, herpes simplex, and coronavirus. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer" *Nat Rev Cancer* 12(7):465-77 (2012). Thus, one aspect of the invention provides compounds, compositions, and methods for treating these inflammatory responses to infections with bacteria, viruses, fungi, parasites, and their toxins described herein.
Cancer is a group of diseases caused by dysregulated cell proliferation. Therapeutic approaches aim to decrease the numbers of cancer cells by inhibiting cell replication or by inducing cancer cell differentiation or death, but there is still significant unmet medical need for more efficacious therapeutic agents. Cancer cells accumulate genetic and epigenetic changes that alter cell growth and metabolism, promoting cell proliferation and increasing resistance to programmed cell death, or apoptosis. Some of these changes include inactivation of tumor suppressor genes, activation of oncogenes, and modifications of the regulation of chromatin structure, including deregulation of histone PTMs. Watson, J.D., "Curing ‘incurable’ cancer," Cancer Discov 1(6):477-80 (2011); Morin, R.D., et al., "Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma" Nature 476(7360):298-303 (2011).


[013] BET inhibitors may be useful in the treatment of benign proliferative and fibrotic disorders, including benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, juvenile polyposis syndrome, idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, and cardiac fibrosis. Tang, X et al., "Assessment of Brd4 Inhibition in Idiopathic Pulmonary Fibrosis Lung Fibroblasts and in Vivo Models of Lung Fibrosis," Am J Pathology in press (2013). Thus, one aspect of the invention provides compounds, compositions, and methods for treating such benign proliferative and fibrotic disorders.


[016] BET inhibitors may be useful in the prevention and treatment of conditions associated with ischemia-reperfusion injury such as, but not limited to, myocardial infarction, stroke, acute coronary syndromes (Prinjha, R.K., J. Witherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains" *Trends Pharmacol Sci* 33(3):146-53 (2012)), renal reperfusion injury, organ transplantation, coronary artery bypass grafting, cardio-pulmonary bypass procedures, hypertension, pulmonary, renal, hepatic, gastro-intestinal, or peripheral limb embolism. Accordingly, one aspect of the invention provides compounds, compositions, and methods for prevention and treatment of conditions described herein that are associated with ischemia-reperfusion injury.


[019] BET inhibitors may be useful in the prevention and treatment of episome-based DNA viruses including, but not limited to, human papillomavirus, herpes virus, Epstein-Barr virus, human immunodeficiency virus (Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," *Nat Rev Cancer* 12(7):465-77 (2012)), adenovirus, poxvirus, hepatitis B virus, and hepatitis C virus. Thus, the invention also provides compounds, compositions, and methods for treatment and prevention of episome-based DNA virus infections described herein.


efficacious approach to male contraception. Thus, another aspect of the invention provides compounds, compositions, and methods for male contraception.


Preclinical data have suggested that small- and large-molecule inhibitors of MCP-1 and CCR2 have potential as therapeu tic agents in inflammatory and autoimmune indications. Thus,
one aspect of the invention provides compounds, compositions, and methods for treating cardiovascular, inflammatory, and autoimmune conditions associated with MCP-1 and CCR2.

[027] Accordingly, the invention provides compounds that are useful for inhibition of BET protein function by binding to bromodomains, pharmaceutical compositions comprising one or more of those compounds, and use of these compounds or compositions in the treatment and prevention of diseases and conditions, including, but not limited to, cancer, autoimmune, and cardiovascular diseases.

[028] The compounds of the invention are defined by Formula I:

\[
\begin{align*}
\text{A} & \quad \text{is a 5-membered monocyclic heterocycle having the formula} \\
Y & \quad \text{and is fused to ring B to form an A-B bicyclic ring,} \\
B & \quad \text{is a six-membered carbocycle or heterocycle;} \\
W_1 & \quad \text{is selected from N and CR;} \\
W_2 & \quad \text{is CR;} \\
W_3 & \quad \text{are C;} \\
R_1 & \quad \text{and R_2 are independently selected from hydrogen, deuterium, alkyl, -OH, -NH_2, -thioalkyl, and alkoxy;} \\
X & \quad \text{is optionally present, and if present, is selected from -(N H)_-, -NHCR_2R_3-, -NH_5G_2-, oxygen, -CH_2CH_2-, -CH=CH-, -CR_2R_3NH-, -GCR_2R_3-, -CR_2R_3O-, -SCR_2R_3-, -CR_2R_3S-, where S might be oxidized to sulfoxide or sulfone, or -NHC(O)_-, wherein the nitrogen is connected to the B ring;}
\end{align*}
\]

...
and $Z_3$ are independently selected from oxygen and -N-R$_3$;

$Y$ is selected from 0 and $S$;

each R$_3$ is independently selected from hydrogen, deuterium, and alkyl(Ci.) (methyl, ethyl, propyl, cyclopropyl);

R$_n$ and R$_s$ are each independently selected from hydrogen, alkyl(Ci.), halogen, -OH, -CF$_3$,
deuterium, amino, aikoxy(Ci$_3$), or two substituents selected from R$_n$. R$_n$ and R$_s$ may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;

R$_s$ is selected from hydrogen, 4-7-membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;

with the proviso that R$_3$ cannot be hydrogen if X is different from -NH-, and

D$_1$ is selected from 5-membered monocyclic carbocycles and heterocycles connected to the 8-member ring via a carbon-carbon bond,

with the proviso that D$_1$ cannot be a substituted or unsubstituted furan, thiophene, cyclopentane, tetrahydrofurane, and tetrahydrothiophene.

[029] Other compounds of the invention are described by Formula IA:

![Formula IA](attachment:image.png)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof,

wherein:

W$_1$ is selected from N and Ci$_4$;

R$_n$ and R$_s$ are independently selected from hydrogen, deuterium, alkyl, -OH, -NH$_2$, -thioalkyl,

and aikoxy;

Y is selected from 0 and $S$;

Z$_3$ and Z$_4$ are independently selected from oxygen and -N-R$_3$;

each R$_n$ is independently selected from hydrogen, deuterium, and alkyl(Ci$_3$) (such as, e.g., methyl, ethyl, propyl, cyclopropyl);
X is optionally present, and if present, is selected from \(-\{\text{NH}\}\), \(-\text{NHCR}_xR_y\), \(-\text{NHSO}_2\), oxygen, \(-\text{CH}_2\text{CH}_3\), \(-\text{CH}=\text{CH}\), \(-\text{CR}_xR_y\text{NH}\), \(-\text{OCR}_xR_y\), \(-\text{CR}_xR_y\text{O}\), \(-\text{SCR}_xR_y\), \(-\text{CR}_xR_y\text{SO}\), where 5 might be oxidized to sulfoxide or sulfone, or \(-\text{NHC}(\text{O})\), wherein the nitrogen is connected to the B ring;

\(R_x\) and \(R_y\) are each independently selected from hydrogen, alkyl(Ci.5), halogen, \(-\text{OH}\), \(-\text{CF}_3\), deuterium, amino, alkoxy(Ci.5), or two substituents selected from \(R_x\), \(R_y\) and \(R_1\) may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;

\(R_3\) is selected from hydrogen, 4-7 membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;

with the proviso that \(R_3\) cannot be hydrogen if \(X\) is different from \(-\text{NH}\), and

\(D_3\) is selected from 5-membered monocyclic carbocycles and heterocycles connected to the B-ring via a carbon-carbon bond,

with the proviso that \(D_1\) cannot be a substituted or unsubstituted furan, thiophene, cyclopentane, tetrahydrofurane, and tetrahydrothiophene.

[030] In another aspect of the invention, a pharmaceutical composition comprising a compound of Formula I, or stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof and one or more pharmaceutically acceptable carriers, diluents or excipients is provided.

[031] In yet another aspect of the invention there is provided a compound of Formula I or Formula IA, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof for use in therapy, in particular in the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

[032] In yet another aspect of the invention there is provided a compound of Formula I or Formula IA, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

**DEFINITIONS**

[033] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout.

[034] As used herein, "cardiovascular disease" refers to diseases, disorders and conditions of the heart and circulatory system that are mediated by BET inhibition. Exemplary cardiovascular diseases, including cholesterol- or lipid-related disorders, include, but are not limited to, acute coronary syndrome, angina, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease,
coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias,
dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, familial combined
hyperlipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hyperbetaalipoproteinemia,
hypercholesterolemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia
reperfusion injury, ischemic heart diseases, cardiac ischemia, metabolic syndrome, multi-infarct
dementia, myocardial infarction, obesity, peripheral vascular disease, reperfusion injury, restenosis,
renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic
attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X, impotence, multiple sclerosis, Parkinson's disease, and inflammatory
diseases.

[035] As used herein, "inflammatory diseases" refers to diseases, disorders, and
conditions that are mediated by BET inhibition. Exemplary inflammatory diseases, include, but are
not limited to, arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and
chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel
diseases, autoimmune diabetes, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy,
ocular inflammation, uveitis, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis,
chronic obstructive pulmonary disease (COPD), glomerulonephritis. Graves disease, gastrointestinal
allergies, conjunctivitis, atherosclerosis, coronary artery disease, angina, and small artery disease.

[036] As used herein, "cancer" refers to diseases, disorders., and conditions that are
mediated by BET inhibition. Exemplary cancers, include, but are not limited to, chronic lymphocytic
leukemia and multiple myeloma, follicular lymphoma, diffuse large B cell lymphoma with germinal
center phenotype, Burkitt's lymphoma, Hodgkin's lymphoma, follicular lymphomas and activated,
anaplastic large cell lymphoma, neuroblastoma and primary neuroectodermal tumor,
rhabdomyosarcoma, prostate cancer, breast cancer, NMC (NUT-midline carcinoma), acute myeloid
leukemia (AML), acute B lymphoblastic leukemia (B-ALL), Burkitt's Lymphoma, B-cell lymphoma,
melanoma, mixed lineage leukemia, multiple myeloma, pro-myelocytic leukemia (PMI), non-
Hodgkin's lymphoma, neuroblastoma, medulloblastoma, lung carcinoma (NSCLC, SCLC), and colon
carcinoma.

[037] "Subject" refers to an animal, such as a mammal, that has been or will be the object
of treatment, observation, or experiment. The methods described herein may be useful for both
human therapy and veterinary applications, in one embodiment, the subject is a human.

[038] As used herein, "treatment" or "treating" refers to an amelioration of a disease or
disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or
"treating" refers to an amelioration of at least one measurable physical parameter, not necessarily
discernible by the patient. In yet another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder. For example, treating a cholesterol disorder may comprise decreasing blood cholesterol levels.

[039] As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder.

[040] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

[041] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" encompasses both "aryl" and "substituted aryl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impossible, synthetically non-feasible and/or inherently unstable.

[042] As used herein, the term "hydrate" refers to a crystal form with either a stoichiometric or non-stoichiometric amount of water incorporated into the crystal structure.

[043] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-8 carbon atoms, referred to herein as (C₂-C₈)alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, alkenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, and 4-(2-methyl-3-butene)-pentenyl.

[044] The term "alkoxy" as used herein refers to an alkyl group attached to an oxygen (-O-alkyl). "Alkoxo" groups also include an alkenyl group attached to an oxygen ("alkenyl oxy") or an alkynyl group attached to an oxygen ("alkynioxy") groups. Exemplary alkoxy groups include, but are not limited to, groups with an alkyl, alkenyl or alkynyl group of 1-8 carbon atoms, referred to herein as (C₃-C₈)alkoxy. Exemplary alkoxy groups include, but are not limited to methoxy and ethoxy.

[045] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-8 carbon atoms, referred to herein as (C₁-C₈)alkyl. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-
methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl.

[046] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-8 carbon atoms, referred to herein as \( (C_2-C_8) \)-alkynyl. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-buty1-2-hexynyl.

[047] The term "amide" as used herein refers to the form -\( NR_3\)C(0)(Rk)- or -C(0)NRbRc-, wherein \( R_3, R_b \) and \( R_c \) are each independently selected from alkyl, alkenyl, aikynyi, ary, arylalkyl, cycloalkyl, haioalkyl, heteroaryl, heterocyci, and hydrogen. The amide can be attached to another group through the carbon, the nitrogen, \( R_b \), or \( R_c \). The amide also may be cyclic, for example \( R_3 \) and \( R_c \) may be joined to form a 3- to 8-membered ring, such as 5- or 6-membered ring. The term "amide" encompasses groups such as sulfonamide, urea, ureido, carbamate, carboxylic acid, and cyclic versions thereof. The term "amide" also encompasses an amide group attached to a carboxy group, e.g., -amide-COOH or salts such as -amide-COONa, an amino group attached to a carboxy group (e.g., -amino-COOH or salts such as -amino-COONa).

[048] The term "amine" or "amino" as used herein refers to the form -\( NR_dR_e \) or -\( N(R_u)R_e \)-, where \( R_d \) and \( R_e \) are independently selected from alkyl, alkenyl, aikynyi, ary, arylalkyl, carbamate, cycloalkyl, haioalkyl, heteroaryl, heterocyci, and hydrogen. The amino can be attached to the parent molecular group through the nitrogen. The amino also may be cyclic, for example any two of \( R_d \) and \( R_e \) may be joined together or with the N to form a 3- to 12-membered ring (e.g., morpholino or psperidinyi). The term amino also includes the corresponding quaternary ammonium salt of any amino group. Exemplary amino groups include alkylamino groups, wherein at least one of \( R_d \) or \( R_e \) is an alkyl group. In some embodiments \( R_d \) and \( R_e \) each may be optionally substituted with one or more hydroxy, halogen, aikxy, ester, or amino.

[049] The term "aryl" as used herein refers to a mono-, bi-, or other multi-carbocyclic, aromatic ring system. The aryl group can optionally be fused to one or more rings selected from aryls, cycloalkyls, and heterocyciys. The aryl groups of this present disclosure can be substituted with groups selected from alkoxy, aryloxy, alkyl, alkenyl, aikynyi, amide, amino, ary, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haioalkyl, heteroaryl, heterocyci, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyi, sulfonyl, sulfonic acid, sulfonamide, and thiokei. Exemplary aryl groups include, but are not limited to, phenyl, toly, anthracenyl, fluoreny, indeny, azuleny, and napthyl, as well as benzo-fused carbocyclic moieties such as
5,6,7,8-tetrahydronaphthyl. Exemplary aryl groups also include, but are not limited to a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryl."

[050] The term "aryalkyl" as used herein refers to an alkyl group having at least one aryl substituent (e.g., -aryl-alkyl-). Exemplary aryalkyl groups include, but are not limited to, arylalkyls having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryalkyl."

[051] The term "carbamate" as used herein refers to the form -RgOC(0)N(R^j)-, -RgOC(0)N(Rh)Rj-, or -OC(0)NRhRj, wherein Rg, Rh, and Rj are each independently selected from alkyl, alkenyl, aikynyl, aryl, aryalkyl, cycloalkyl, heteroaryl, heterocyclyl, and hydrogen. Exemplary carbamates include, but are not limited to, arylicarbamates or heteroarylcarbamates (e.g., wherein at least one of Rg, Rh, and Rj are independently selected from aryl or heteroaryl, such as pyridine, pyridazine, pyrimidine, and pyrazine).

[052] The term "carbocycle" as used herein refers to an aryl or cycloalkyl group.

[053] The term "carboxy" as used herein refers to -COOH or its corresponding carboxylate salts (e.g., -COONa). The term carboxy also includes "carboxycarbonyl," e.g. a carboxy group attached to a carboxy group, e.g., -C(0)-COOH or salts, such as -C(0)-COONa.

[054] The term "cyano" as used herein refers to -CM

[055] The term "cyloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen.

[058] The term "cycloalkyl" as used herein refers to a saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-12 carbons, or 3-8 carbons, referred to herein as "(C₃-C₈)cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenes. Cycloalkyl groups may be substituted with aikynyl, aryloxy, alkyl, alkenyl, aikynyl, amide, amino, aryl, aryalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyS, halogen, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfiny, sulfony, sulfonic acid, sulfonamide and thioketone.

Cycloalkyl groups can be fused to other cycloalkyl saturated or unsaturated, aryl, or heterocyclyl groups.

[057] The term "dicarboxylic acid" as used herein refers to a group containing at least two carboxylic acid groups such as saturated and unsaturated hydrocarbon dicarboxylic acids and salts thereof. Exemplary dicarboxylic acids include alkyl dicarboxylic acids. Dicarboxylic acids may be substituted with aikynyl, aryloxy, alkyl, alkenyl, aikynyl, amide, amino, aryl, aryalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyS, halogen, heteroalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfiny, sulfony, sulfonic acid, sulfonamide
and thioketone. Dicarboxylic acids include, but are not limited to succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, maleic acid, phthalic acid, aspartic acid, glutamic acid, malonic acid, fumaric acid, (+)/(-)-malic acid, (+)/(-) tartaric acid, isophthalic acid, and terephthalic acid. Dicarboxylic acids further include carboxylic acid derivatives thereof, such as anhydrides, imides, hydrazides (for example, succinic anhydride and succinimide).

[058] The term "ester" refers to the structure -C(0)0-, -C(0)0-R_j-, -R_kC(0)0-R_j-, or -R^C(O)O-, where 0 is not bound to hydrogen, and R_j and R_k can independently be selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, cycloalkyl, ether, haloalkyl, heteroaryl, and heterocycyl. R_k can be a hydrogen, but R_j cannot be hydrogen. The ester may be cyclic, for example the carbon atom and R_j the oxygen atom and R_k or R_j and R_k may be joined to form a 3- to 12-membered ring. Exemplary esters include, but are not limited to, alkyl esters wherein at least one of R_j or R_k is alkyl, such as -O-C(0)-alkyi, -C(0)-0-alkyi- and -alkyl-C(0)-0-alkyi-.

Exemplary esters also include aryl or heteroaryl esters, e.g. wherein at least one of R_j or R_k is a heteroaryl group such as pyridine, pyrazidine, pyrimidine and pyrazine, such as a nicotinate ester. Exemplary esters also include reverse esters having the structure -R^C(O)O-, where the oxygen is bound to the parent molecule. Exemplary reverse esters include succinate, D-argininate, L-argininate, L-lysinate and D-lysinate. Esters also include carboxylic acid anhydrides and acid halides.

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

[060] The term "heteroalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms. "Haloalkyi" also encompass alkenyl or alkynyl groups substituted with one or more halogen atoms.

[061] The term "heteroaryl" as used herein refers to a mono-, bi-, or multi-cyclic, aromatic ring system containing one or more heteroatoms, for example 1-3 heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroaryls can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formy, halogen, haloalkyi, heteroaryl, heterocycyl, hydroxy, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heteroaryls can also be fused to non-aromatic rings. Illustrative examples of heteroaryl groups include, but are not limited to, pyridiniyi, pyridazinyli, pyrimidyli, pyrazyli, triazynyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyli, pyrazinyl, pyrimidyli, tetrazolyli, furyli, thiényli, isoxazo/yl, thiazolyl, furyl, phenyl, isoxazo/yl, and oxazo/yl. Exemplary heteroaryl groups include, but are not limited to, a monocyclic aromatic ring, wherein the ring comprises 2-5 carbon atoms and 1-3 heteroatoms, referred to herein as "[C_2-C_5]heteroaryl."
The terms "heterocyclic," "heterocyclyl," or "heterocyclic" as used herein refer to a saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered ring containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur. Heterocycles can be aromatic (heteroaryl)s or non-aromatic. Heterocycles can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, aikenyi, alkynyl, amide, amino, aryl, arylaikyl, carbamate, carboxy, eyano, cycloalkyi, ester, ether, formyl, halogen, haloaikyl, heteroaryl, heterocyclyl, hydroxy, ketone, nitro, phosphate, sulfide, sulfinyi, sulfonyl, sulfonic acid, sulfonamide, and thioketone.

Heterocycles also include bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from aryls, cycloalkyls, and heterocycles. Exemplary heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoaxazolyl, biotinyi, cinnoinyi, dihydrofuryl, dihydroindolyl, dihydropyranyi, dicydrothienyi, dithiazolyl, furyl, homopiperidinyi, imidazolinyi, imidazolinyl, imidazolyi, indolyl, isoquinolyl, isothiazolinyi, isothiazoyi, isoxazolinyi, isoxazolyl, morpholinyi, oxadiazoliyi, oxazolidinyi, oxazolyl, piperazinyi, piperidinyi, pyranyl, pyrazolinyi, pyrazinyi, pyrazoinyi, pyridazinyi, pyridyl, pyrimidinyi, pyrimidyl, pyrrolinyi, pyrrolidinyi, pyrrolidin-2-onyl, pyrydinyi, pyrydinyi, quinolinyl, quinoxalolyl, tetrahydrofuryl, tetrahydroisoquintolyl, tetrahydropyranS, tetrahydroquinolinyi, tetrazolyl, thia diazolinyi, thiazolinyi, thiazyloyi, thienyl, thiomorpholinyi, thiopyranyi, and triaizoiy.

The terms "hydroxy" and "hydroxy!" as used herein refer to -OH.

The term "hydroxyalkyl" as used herein refers to a hydroxy attached to an alkyl group.

The term "hydroxyary!" as used herein refers to a hydroxy attached to an aryl group.

The term "ketone" as used herein refers to the structure -C(0)-Rn (such as acetyl, -C(0)CH3) or -Rn.C(0).R0.. The ketone can be attached to another group through Rn or R0. Rn or R0 can be alkyl, aikenyi, alkynyl, cycloalkyi, heterocyclyl or aryl, or Rn or R0 can be joined to form a 3- to 12-membered ring.

The term "monoor ester" as used herein refers to an analogue of a dicarboxylic acid wherein one of the carboxyiic acids is functionalized as an ester and the other carboxyiic acid is a free carboxyiic acid or salt of a carboxyiic acid. Examples of monooesters include, but are not limited to, to monooesters of succinic acid, glutaiic acid, adipic acid, suberic acid, sebacic acid, azeiaic acid, oxalic and maleic acid.

The term "phenyl" as used herein refers to a 6-membered carbocyclic aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. Phenyl can be
substituted with one or more substituents including alkoxy, aryloxy, alkyi, aikynyi, amide, amino, aryl, aryalkyl, carbamate, carboxy, cyano, cycioalkyl, ester, ether, formyi, halogen, haloalkyl, heteroaryi, heterocyciyl, hydroxyi, ketone, phosphate, sulfide, sulfinyi, sulfonyl, sulfonic acid, sulfonamide and thioketone.

[069] The term "thioalkyl" as used herein refers to an alkiy group attached to a sulfur (-S-alkyl).

[070] "Alkiy," "aikenyi," "alkoxy," "amino" and "amide" groups can be optionally substituted with or interrupted by or branched with at least one group selected from alkoxy, aryloxy, aiikenyi, aikenyi, amide, amino, aryl, aryalkyi, carbamate, carbonyl, carboxy, cyano, cycioalkyi, ester, ether, formyi, halogen, haloalkyi, heteroaryi, heterocyciyl, hydroxyi, ketone, phosphate, sulfide, sulfinyi, sulfonyl, sulfonic acid, sulfonamide, thiokeke, thioketone, ureido and N. The substituents may be branched to form a substituted or unsubstituted heterocycle or cycioalkyi.

[071] As used herein, a suitable substitution on an optionally substituted substituent refers to a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the present disclosure or the intermediates useful for preparing them. Examples of suitable substitutions include, but are not limited to: C<sub>3</sub>-alkyi, aiikenyi or alkynyi; C<sub>M</sub> aryl, C<sub>2</sub>-heteroaryi; C<sub>2</sub>-cycioalkyi; C<sub>3,6</sub> aikeyo; C<sub>6</sub> aryloxy; -CN; -OH; oxo; halo, carboxy; amino, such as -NH(C<sub>1</sub>-alkyi), -N(Cl<sub>1</sub>-alkyi) -NH((Cl<sub>6</sub> aryi)); or N((Cl<sub>6</sub> aryi)); formyi; ketones, such as -CO(Cl<sub>1</sub>-alkyi), -CO((Cl<sub>6</sub> aryi)); esters, such as -CO<sub>2</sub>(C<sub>1</sub>-alkyi) and -CO<sub>2</sub>(C<sub>6</sub> aryi). One of skill in art can readily choose a suitable substitution based on the stabiliiy and pharmacological and synthetic activity of the compound of the present disclosure.

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

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

[074] The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present disclosure that 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, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds.

[075] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to sulfate, citrate, matate, acetate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisate, fumarate, gluconate, glucarionate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., L,l'-methylen-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

[076] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[077] Individual stereoisomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a
mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[078] Geometric isomers can also exist in the compounds of the present disclosure. The present disclosure encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the E and Z isomers.

[079] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangements of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[080] The compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the present disclosure, even though only one tautomeric structure is depicted.

EXEMPLARY EMBODIMENTS OF THE INVENTION

[081] The invention provides compounds and pharmaceutical composition comprising one or more of those compounds wherein the structure of the compound is defined by Formula I:
or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof,

wherein:

A is a 5-membered monocyclic heterocycle having the formula
and is fused to ring S to form an A-B bicyclic ring,

S is a six-membered carbocycle or heterocycle;

W₁ is selected from N and CR₁;

W₂ is CR₂;

W₃ and W₄ are C;

Y is selected from O and S;

Z₁ and Z₂ are independently selected from oxygen and -N·R₄;

each R₄ is independently selected from hydrogen, deuterium, and alkyl(C₃₋₅) (methyl, ethyl, propyl, cyclopropyl);

R₅ and R₆ are independently selected from hydrogen, deuterium, alkyl, -OH, -NH₂, -thioalkyl, and alkoxy;

X is optionally present, and if present, is selected from -(NH) -, -NHCR₄R₅-, -NHSO₂-, oxygen, -CH₂CH₂-, -CH=CH-, -CR₄R₅NH-, -OCR₁R₂-, -CR₄R₅O-, -SCR₁R₂-, -CR₄R₅S-, where S might be oxidized to sulfoxide or sulfone, or -NHC(=O)-, wherein the nitrogen is connected to the S ring;

R₇ and R₈ are each independently selected from hydrogen, alkyl(C₄₋₅), halogen, -OH, -CF₃, deuterium, amino, alkoxy(C₄₋₅), or two substituents selected from R₇, R₈, and ¾ may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;

R₉ is selected from hydrogen, 4-7 membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;

with the proviso that R₉ cannot be hydrogen if X is different from -NH-, and
$D_1$ is selected from 5-membered monocyclic carbocycles and heterocycles connected to the B-ring via a carbon-carbon bond,

with the proviso that $D$ cannot be a substituted or unsubstituted furan, thiophene, cyclopentane, tetrahydrofurane, and tetrahydrothiophene.

[082] In some embodiments of Formula i, the A-B ring is a substituted or unsubstituted

![Chemical structure](image)

[083] In some embodiments, provided is a compound of Formula 1A:

![Chemical structure](image)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof,

wherein:

- $W_1$ is selected from $N$ and $CR_3$;
- $R_1$ and $R_2$ are independently selected from hydrogen, deuterium, alkyl, -OH, -NH$_2$, -thioalkyl, arsd alkoxy;
- $Y$ is selected from $O$ and $S$;
- $Z_1$ and $Z_2$ are independently selected from oxygen and -N-$R_3$;
- each $R_3$ is independently selected from hydrogen, deuterium, and alky!(Ci.) (such as, e.g., methyl, ethyl, propyl, cyclopropyl);
- $X$ is optionally present, and if present, is selected from ~(NH) -.NHCR$_x$R$_y$. -NHSO$_2$-. oxygen, -CH$_2$CH$_2$-. -CH=CH-. -CR$_x$R$_y$NH-. -OCR$_x$R$_y$. -CR$_x$R$_y$O-. -SCR$_x$R$_y$. -CR$_x$R$_y$S-. where S might be oxidized to sulfoxide or sulfone, or -NHC(O)-, wherein the nitrogen is connected to the B ring;
- $R_1$ and $R_2$ are each independently selected from hydrogen, alky!(Ci.), halogen, -OH, -CF$_3$, deuterium, amino, alkoxy(Ci.), or two substituents selected from $R_3$, $R_4$, and $R_5$ may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;
- $R_6$ is selected from hydrogen, 4-7 membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;
with the proviso that $R_3$ cannot be hydrogen if $X$ is different from -NH-, and
$D_3$ is selected from 5-membered monocyclic carbocycles and heterocycles connected to the
B-ring via a carbon-carbon bond,

with the proviso that $D_3$ cannot be a substituted or unsubstituted furan, thiophene,
cyclopentane, tetrahydrofurane, and tetrahydrothiophene.

[084] In some embodiments of Formula IA, the A-B bicyclic ring is selected from

![Diagram 1]

and

[085] In certain embodiments of Formula IA, the A-B bicyclic ring is selected from

![Diagram 2]

and

[086] In some embodiments of Formula IA, the A-B bicyclic ring is selected from

![Diagram 3]

[087] In some embodiments of Formula IA, the A-B bicyclic ring is selected from

![Diagram 4]
In some embodiments of Formula IA, R₂ is selected from hydrogen and methyl.

In some embodiments of Formula IA, one or more hydrogen atoms is replaced with deuterium.

In certain embodiments of Formula IA, D₁ is selected from a 5-membered monocyclic heterocycle selected from

wherein the D₁ ring is optionally substituted with one or more deuterium, alkyl(C₅₋₆) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C₁₋₄) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH₂, -NHMe, -NHEt, -NHPr, -NHBu, -NMMe₂, -NMeEt, -NMePr, -NMeBu), halogen (such as F, Cl, Br, -OH, -NH₂, -NMe₂, -OMe, -SMe, -OEt, -SPr, -SBu, -COOH, and/or ester (such as COOEt, -C(O)OEt, -C(O)OBu), wherein said alkyl(C₁₋₆), alkoxy(C₁₋₆), amino, amide, ketone (C₁₋₆), -S(O)alkyl(C₁₋₆), -S(O₂)alkyl(C₁₋₆), -thioalkyl(C₁₋₆), and ester may be optionally substituted with one or more F, Cl, Br, -OH, -NH₂, -NMe₂, -OMe, -SMe, oxo, and/or thio-oxo. In certain embodiments D₁ is optionally substituted with one or more deuterium, and C₁₋₃alkyl.

In some embodiments of Formula IA, D₁ is selected from a 5-membered monocyclic heterocycle selected from

optionally substituted with one or more deuterium, alkyHC₅₋₆) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C₁₋₆) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH₂, -NHMe, -NHEt, -NHPr, -NHBu, -NMMe₂, -NMeEt, -NMePr, -NMeBu), halogen (such as F, Cl, Br, -OH, -NH₂, -NMe₂, -OMe, -SMe, -OEt, -SPr, -SBu, -COOH, and/or
ester (such as -C(0)OMe, -C(0)OBt, -C(O)OBu), wherein said alkyl(C<sub>1</sub>-C<sub>4</sub>), alkoxy(C<sub>1</sub>-C<sub>4</sub>), amino, amide, ketone (C<sub>1</sub>-Q), -S(0)alkyl(C<sub>1</sub>-C<sub>4</sub>), -S<sub>2</sub>alkyl[(CrC<sub>4</sub>), -thioalkyl(C<sub>1</sub>-C<sub>4</sub>), and ester may be optionally substituted with one or more F, Cl, Br, -OH, -NH<sub>2</sub>, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo. In certain embodiments, D<sub>2</sub> is optionally substituted with one or more deuterium, and C<sub>1</sub>-C<sub>4</sub>alkyl such as methyl.

[092] In certain embodiments of Formula IA, D<sub>2</sub> is optionally substituted with one or more deuterium, alkyl(C<sub>1</sub>-C<sub>4</sub>)[such as methyl, ethyl, propyl, isopropyl, butyl], alkoxy(C<sub>1</sub>-C<sub>4</sub>) (such as methoxy, ethoxy, isoproxy), wherein said alkyl(C<sub>1</sub>-C<sub>4</sub>) and alkoxy(C<sub>1</sub>-C<sub>4</sub>) may be optionally substituted with one or more F, Cl, Br, -OH, or -NH<sub>2</sub>.

[093] In other embodiments of Formula IA, D<sub>2</sub> is selected from a 5-membered monocyclic heterocycle containing one oxygen and one or two nitrogens, where the heterocycle is connected to the rest of the molecule via a carbon-carbon bond, optionally substituted with one or more hydrogen, deuterium, alkyl(C<sub>1</sub>-C<sub>4</sub>)[such as methyl, ethyl, propyl, isopropyl, butyl], each of which may be optionally substituted with one or more F, Cl, Br, -OH, or -NH<sub>2</sub>.

[094] In certain embodiments of Formula IA, D<sub>2</sub> is an isoxazole or pyrazole optionally substituted with one or more deuterium, alkyl(C<sub>1</sub>-C<sub>4</sub>)[such as methyl, ethyl, propyl, isopropyl, butyl], wherein said alkyl(C<sub>1</sub>-C<sub>4</sub>) may be optionally substituted with one or more F, -OH, or -NH<sub>2</sub>.

[095] In some embodiments of Formula IA, D<sub>2</sub> is an isoxazole optionally substituted with one or more one or two groups independently selected from deuterium, alkyl(CrC<sub>4</sub>)(such as methyl, ethyl, propyl, isopropyl, butyl), wherein said alkyl(CrC<sub>4</sub>) may be optionally substituted with one or more F, -OH, or -NH<sub>2</sub>.

[096] In some embodiments of Formula IA, D<sub>3</sub> is.

[097] In some embodiments of Formula IA, Z<sub>1</sub> is -NRa, and Ra is methyl.

[098] In certain embodiments of Formula IA, Z<sub>2</sub> is oxygen.

[099] In certain embodiments of Formula IA, W<sub>1</sub> is CR<sub>2</sub>.

[100] In some embodiments of Formula IA, X is optionally present, and if present, is selected from -{NH}·, -NHCR<sub>2</sub>R<sub>1</sub>·, -NHSO<sub>2</sub>·, oxygen, -CH<sub>2</sub>CH<sub>2</sub>·, -CH=CH·, -CR<sub>r</sub>R<sub>1</sub>NH·, -OCR<sub>2</sub>R<sub>1</sub>·, -CR<sub>r</sub>R<sub>1</sub>O·, -SCR<sub>2</sub>·, where S might be oxidized to sulfoxide or sulfone, or -IMH(C)(O)·, wherein the nitrogen is connected to the B ring. In some embodiments, X is optionally present, and if present, is selected from -{(NH)·, -NHCR<sub>r</sub>R<sub>1</sub>·, -CR<sub>r</sub>R<sub>1</sub>NH·.

[101] In certain embodiments of Formula IA, X is not present.

[102] In some embodiments of Formula IA, X is oxygen.

[103] In some embodiments of Formula IA, X is -NH· and R<sub>5</sub> is hydrogen.
In other embodiments of Formula I A, R₄ and R₅ are each independently selected from hydrogen, alkyl(C₅₋₉), halogen, -OH, -CF₃, deuterium, amino, and alkoxy(C₆₋₉). In some embodiments, R₄ and R₅ are each independently selected from hydrogen, methyl, halogen, -CF₃ and deuterium.

In some embodiments of Formula I A, R₃ is selected from hydrogen, deuterium, alkyl, -OH, and -NH₂. In certain embodiments of Formula I A, R₃ is selected from hydrogen and methoxy. In certain embodiments of Formula I A, R₃ is selected from hydrogen, deuterium, -NH₂, and methyl. In some embodiments of Formula I A, R₃ is hydrogen.

In other embodiments of Formula I A, R₂ is selected from hydrogen, -Br, and -NH₂.

In some embodiments of Formula I A, R₃ is selected from 5-6 membered carbocycles, 5-6-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles. In certain embodiments of Formula I A, R₃ is selected from 5-6 membered heterocycles. In certain embodiments of Formula I A, R₃ is selected from 5-6 membered heterocycles containing 1 or 2 nitrogens, such as unsubstituted and substituted pyrimidyl rings. In some embodiments of Formula I A, R₃ is selected from 6-membered heterocycles containing at least one nitrogen, such as unsubstituted and substituted pyridyl rings.

In some embodiments of Formula I A, R₃ is selected from optionally substituted with one or more groups independently selected from deuterium, alkyl(C₅₋₉) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C₆₋₉) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH₂, -NHMe, -NHEt, -NHiPr, -NHBU -NMe₂, -NMe₂ -NBU -NHC(O)NHalkyl), halogen (such as F, Cl), amide (such as -NHCO(0)Me, -NHCO(0)Et, -C(0)NH₂, -C(0)NHMe, -C(0)NEt₂, -C(O)NiPr), -CF₃, CN, -N₉, ketone (C₅₋₉) (such as as acetyl, -C(0)Et, -C(O)Pr), -S(0)Alkyl(C₅₋₉) (such as -S(0)Me, -S(O)Et, -SO₂alkyl(C₅₋₉ (such as -SO₂Me, -SO₂Et, -SO₂Pr), -
thioalkyl (C₅₋₆), such as -SMe, -SEt, -SPr, -SBu, carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyl(C₁₋₄), alkoxy(C₁₋₄), amino, amide, ketone (C₁₋₄), -S(0)Alkyl(C₁₋₄), -Sₐθ₂alkyl(C₁₋₄), -thioalkyl(C₁₋₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0109] In certain embodiments of Formula IA, R₃ is selected from

![Image of molecular structures]

 optionally substituted with one or more groups independently selected from deuterium, alkyl(C₁₋₄), (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C₁₋₄), (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NMe, -NHiPr, -NH Bu -NMe₂, -NET₂, -NETBu, -NHC(O)N Halkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)Me₂, -C(O)NHMe, -C(O)N H₃, -C(0)NMe₂, -C(0)N H₂, -C(0)NHMe, -C(0)N Et₂, -C(0)N NiPr), -CF₃, CN, -N₃, ketone (C₁₋₄), (such as acetyl, -C(0)Et, -C(O)Pr), -S(0)Alkyl(C₁₋₄), -S(0)Me, -S(O)Et, -S₀₂alkyl(CrC₄), (such as -S₀₂Me, -S₀₂Et, -SQ₂Pr), -thioalkyl(C₁₋₄), (such as -SMe, -SEt, -SPr, -SBu), carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyl(C₁₋₄), alkoxy(C₁₋₄), amino, amide, ketone (C₁₋₄), -S(0)Alkyl(C₁₋₄), -S₀₂alkyl(C₁₋₄), -thioalkyl(CrC₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0110] In certain embodiments of Formula IA, R₃ is an isoxazolyl or pyrazole optionally substituted with one or more groups independently selected from deuterium, alkyl(C₁₋₄), (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C₁₋₄), (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NMe, -NHiPr, -NH Bu -NMe₂, -NMeEt, -NET₂, -NETBu, -NHC(O)N Halkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NHMe, -C(O)N H₃, -C(0)NHMe, -C(0)N Et₂, -C(0)N NiPr), -CF₃, CN, -N₃, ketone (C₁₋₄), (such as acetyl, -C(0)Et, -C(O)Pr), -S(0)Alkyl(C₁₋₄), -S(0)Me, -S(O)Et, -S₀₂alkyl(CrC₄), (such as -S₀₂Me, -S₀₂Et, -SQ₂Pr), -thioalkyl(C₁₋₄), (such as -SMe, -SEt, -SPr, -SBu), carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyl(C₁₋₄), alkoxy(C₁₋₄), amino, amide, ketone (C₁₋₄), -S(0)Alkyl(C₁₋₄), -S₀₂alkyl(C₁₋₄), -thioalkyl(CrC₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0111] In some embodiments of Formula IA, R₃ is selected from 5-6 membered carbocycles, such as a substituted or unsubstituted phenyl ring. In certain embodiments R₃ is a 5-6 membered carbocycle substituted with a group selected from Methyl, -CF₃, -OCF₃, -OMe, -QEt, MeOCH₂-, -Cl, -F, -CN, -NH₂, -C(O)NH₂, -C(O)NHMe, -NHC(O)CH3, N,N-dimethylaminomethyl, -SO₂Me, and oxo.

[0112] In some embodiments of Formula IA, R₃ is an isoxazolyl, oxazolyl, pyrazolyl, pyridyl, pyridonyl, thiazolyl, isothiazolyl, pyrimidinyl, thiozol, pyraziny, pyridazinyl, azetidinyl, pyrrolidyl, piperidinyl, morpholinyl, cyclopropyl, cyclobutyi, cyclopentyl, cyclohexyl or phenyl optionally substituted with one or more groups independently selected from hydrogen, deuterium, alkyl(C₁₋₄), (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C₁₋₄), (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NMe, -NHiPr, -NH Bu -NMe₂, -NMeEt, -NET₂, -NETBu, -NHC(O)N Halkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NHMe, -C(O)N H₃, -C(0)NHMe, -C(0)N Et₂, -C(0)N NiPr), -CF₃, CN, -N₃, ketone (C₁₋₄), (such as acetyl, -C(0)Et, -C(O)Pr), -S(0)Alkyl(C₁₋₄), -S(0)Me, -S(O)Et, -S₀₂alkyl(CrC₄), (such as -S₀₂Me, -S₀₂Et, -SQ₂Pr), -thioalkyl(C₁₋₄), (such as -SMe, -SEt, -SPr, -SBu), carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyl(C₁₋₄), alkoxy(C₁₋₄), amino, amide, ketone (C₁₋₄), -S(0)Alkyl(C₁₋₄), -S₀₂alkyl(C₁₋₄), -thioalkyl(CrC₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NMe, -OMe, -SMe, oxo, and/or thio-oxo.
NHCalkyl), halogen (such as F, Cl, amide (such as NHCMe, NHCEt, CN, ketone (C1-C4) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C1-C4), (such as -S(0)Me, -S(0)Et), -SO2alkyl(C1-C4) (such as -SO2Me, -SO2Et, -SO2Pr), -thioalkyl(C1-C4) (such as -SMe, -SEt, -SPr, -SBu), carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -NHCalkyl, and/or thio-oxo, C(0)OBu), each of which may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NHMe, oxo, and/or thio-oxo.

In some embodiments of Formula IA, R3 is optionally substituted with one or more methyl, CF3, -OCF3, methoxy, ethoxy, methoxymethyl, CN, F, -NH2, amide (-CONH2, -CONHMMe, -NHCOC(OBu), COOH, -CONMe, N,N-dimethylaminomethyl, -SO2Me, and oxo.

In certain embodiments of Formula IA, R3 is selected from

Optionally substituted with one or more groups independently selected from deuterium, alkyl(C1-C4)(sil/Ch as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C1-C4) (such as methoxy, ethoxy, isoproxy), amino (such as -NH2, -NHMe, -NHEt, -NHPr, -NHBU -NMe2, NMeEt, -NEt2, -NEtBu, -NHCalkyl), halogen (such as F, Cl), amide (such as NHCMe, -NHC(0)Et, -C(0)N HMMe, -C(0)NEt2, -C(O)NiPr), -CF3 CN, -N3, ketone (C1-C4) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C1-C4), (such as -S(0)Me, -S(0)Et), -SO2alkyl(C1-C4) (such as -SO2Me, -SO2Et, -SO2Pr), -thioalkyl(C1-C4) (such as -SMe, -Sft, -SPr, -SBu), carboxyl (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyl(C1-C4), alkoxy(C1-C4), amino, amide, ketone (C1-C4), -S(0)Alkyl(C1-C4), -SO2alkyl(C1-C4), -thioalkyl(C1-C4), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.
[0114] In certain embodiments of Formula IA, R₃ is selected from

![Diagram](image1)

[0115] in some embodiments of Formula IA, -X-R₃ is selected from -NHAryl.

[0116] in certain embodiments of Formula IA, R₃ is pyridyl.

[0117] in some embodiments of Formula IA, the A-B bicyclic ring is selected from

![Diagram](image2)

Dj is an isoxazole or pyrazole optionally substituted with one or more deuterium, alkyl(C₁-C₄)(such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C₃-C₆) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH₂, -NHMe, -NHEt, -NHPr, -NHBu -NMe₂, NMeEt, -NEt₂, -NEtBu, -NHC(O)(N Halkyl)), halogen (such as F, Cl), amide (such as -NHC(O)(Me), -NHC(O)(Et), -C(O)N Me, -C(O)N Et, -C(O)N Pr, -C(O)N Bu), -S(0)alkyl(C₃-C₆), -S(0)alkyloxy(C₃-C₆) (such as -S(0)Me, -S(0)Et, -S(0)Pr, -S(0)Bu), -S0₂alkyl(C₁-C₄) (such as -S0₂Me, -S0₂Et, -S0₂Pr, -S0₂Bu), -thioalkyl(C₁-C₄) (such as -SMe, -SEt, -SPr, -SBU), -COOH, and/or ester (such as -C(0)QMe, -C(0)QEt, -C(0)QOBu), wherein said 3alkyl(CrC₃), alkoxy(C₁-C₄), amino, amide, ketone (C₁-C₄), -S(0)Alkyl(C₁-C₄), -S0₂alkyl(C₁-C₄), -thioalkyl(C₁-C₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OEt, oxo, and/or thio-oxo;

X is optionally present, and if present, is selected from -N(H)-, -0-, -NHC(R₃)₄, -NHS0₂-, and -CRₓRᵧNH; and

Z₁ is -NRₐ; and

R₉ is an isoxazole, pyrazole, pyridyl, thiazole, isothiazole, pyrimidine, phenyl, cyclohexene, benzo[d]oxazolyl, naphthyl, or quinolyl, optionally substituted with one or more groups independently selected from deuterium, alkyl(C₁-C₄)(such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C₁-C₄) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH₂, -NHMe, -NHEt, -NHPr, -NHBu -NMe₂, NMeEt, -NEt₂, -NEtBu, -NHC(O)(N Halkyl)), halogen (such as F, Cl), amide (such as -NHC(O)(Me), -NHC(O)(Et), -C(O)N Me, -C(O)N Et, -C(O)N Pr, -C(O)N Bu), -S(0)alkyl(C₃-C₆), -S(0)alkyloxy(C₃-C₆) (such as -S(0)Me, -S(0)Et, -S(0)Pr, -S(0)Bu), -S0₂alkyl(C₁-C₄) (such as -S0₂Me, -S0₂Et, -S0₂Pr, -S0₂Bu), -thioalkyl(C₁-C₄) (such as -SMe, -SEt, -SPr, -SBU), -COOH, and/or ester (such as -C(0)QMe, -C(0)QEt, -C(0)QOBu), wherein said alkyl(C₁-C₄), alkoxy(C₁-C₄), amino, amide, ketone (C₁-C₄), -S(0)Alkyl(C₁-C₄), -S0₂alkyl(C₁-C₄), -thioalkyl(C₁-C₄), and ester may be optionally substituted.
with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo. In some embodiments, when X is - (NH)- then R₃ may be hydrogen. Alternatively, R₃ is selected from

![Chemical structures](image)

optionally substituted with one or more groups independently selected from deuterium, alkyl(C₄₋₅H₄)(such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C₄₋₅H₄)(such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NHMe, -NHEt, -NHPr, -NHBu, -NMMe₂, -NMeEt, -NEt₂, -NEtBu, -NHC(O)NHAlkyI), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NH₂, -C(0)NHMe, -C(0)NET₂, -C(O)NiPr), -C(0)cycloamino, -CF₃, -CN, -S(O)₂Et, -S(O)₂Pr), -thioalkyl (C₄₋₅H₄)(such as -SMe, -SEt, -SPr, -SBu), -COOH, and/or ester (such as -C(0)OMe, -C(0)OEt, -C(0)OBu), wherein said alkyI(C₄₋₅H₄), alkoxy(C₄₋₅H₄), amino, amide, ketone (C₄₋₅H₄), -S(O)₂AlkyI(C₄₋₅H₄), -SO₂alkyl(Cl₅₋₆H₄), -thioalkyl (C₄₋₅H₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo;

X is optionally present, and if present, is selected from -(N H)-, -NHC₄, -NHSO₂-, -CR₄₅R₂₆NH-, or -NΗ₂ and R₃ is absent; and

R₃ is an isoxazole, pyrazole, puridyl, thiazole, pyrimidine, or phenyl optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo;
carboxyl (such as -COOH), and/or ester (such as -C(O)OMe, -C(O)OEt, -C(Q)OBu), wherein said alkyl(C1-C4), alkoxy (C1-C4), amino, amide, ketone (C2-C4), -SO2alkyl(C1-C4), -thioalkyl(CrQ), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH2, -NHMe, -OME, -SMe, oxo, and/or thio-oxo.

[0119] In certain embodiments of Formula IA, the A-B bicyclic ring is

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{X} \\
\text{O} \\
\text{H} \\
\text{D}_1 \\
\text{N} \\
\text{O} \\
\end{array}
\]

X is absent; and

R5 is an isoxazol, pyrazole, or pyridyl optionally substituted with one or more groups independently selected from deuterium, alkyl(C1-G) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C1-C4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH2, -NHMe, -NHEt, -NHiPr, -NHBu -NMMe2, -NMMe2, -NEt2, -NEtBu, -NHC(O)NHalkyl), halogen (such as F, Cl), -CF3.

[0120] In some embodiments of Formula IA, the compound is selected from:

4.6- bis(3,5-dimethylisoxazol-4-yl)-IH-benzo[d]imidazo[2(3H)-one;
5.7- bis(3,5-dimethyl isoxazol-4-yl)-1-methyl-IH-benzimidazo[2(3H)-one;
5.7-bis(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-methyl pyridin-3-yl)-IH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-(trifluoromethyl)phenyl)-IH-benzimidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-(trifluoromethyl)phenyl)-IH-benzimidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-(trifluoromethyl)phenyl)-IH-benzimidazo[2(3H)-one;
7-(1,3-dimethyl-IH-pyrazol-4-yl)5-(3,5-dimethylisoxazol-4-yl)-1-methyl-IH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-(trifluoromethyl)pyridin-3-yl)-IH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-(trifluoromethyl)pyridin-3-yl)-IH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(l,3,5-trimethyl-IH-pyrazol-4-yl)-IH-benzo[d]imidazo[2(3H)-one;
5-{3,5-dimethylisoxazol-4-yl}-1-methyl-7-(4^-ethylisothiazol-5-yl)-1H-benzo[d]imidazo-
2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-1-methyl-1H-
benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-methoxy-5-methylphenyl)-1-methyl-1H-benzo[d]imidazo-
2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-methoxypyridin-3-yl)-1-methyl-1H-benzo[d]imidazo-
2(3H)-one;
3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo-[d]imidazo-
2(3H)-one;
4,6-bis(3,5-dimethylisoxazol-4-yl)-1,3-dimethyl-1H-benzo[d]imidazo[2(3H)-one;
3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazo-
4,6-methylbenzonitrile;
5-(3,5-dimethylisoxazol-4-yl)-7-(4-methoxy-2-pyridinyl)-1-methyl-1H-benzo[d]imidazo-
2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(5-chloro-2-methylphenyl)-1-methyl-1H-benzo[d]imidazo-
2(3H)-one;
7-(5-chloro-2-methylphenyl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazo-
2(3H)-one;
7-(6-amino-2-methylpyridin-3-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-
benzo[d]imidazo[2(3H)-one;
7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-
benzo[d]imidazo[2(3H)-one;
6-(3,5-dimethylisoxazol-4-yl)-4-(13,5-trimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazo-
2(3H)-thione;
6-(3,5-dimethylisoxazol-4-yl)-4-(4-methylpyridin-3-yl)-1H-benzo[d]imidazo-
2(3H)-thione;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)amino)-1H-
benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-methylpyridin-3-yl)amino)-1H-
benzo[d]imidazo[2(3H)-one;
S-{S-(Hydroxymethyl)-3-methylisoxazol-4-yl)-l-methyl-7-{1,3,5-trimethyl-1H-pyrazol-4-yl)-lH-benzo[d]imidazoi-2(3H)-one;
3-{6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-4-methylbenzamide;
3-{S-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-methylbenzamide;
5-{3,5-dimethylisoxazol-4-yl)-l-methyl-7-{(2-methylpyridin-3-yl)oxy)-lH-benzo[d]imidazoi-2(3H)-one;
7-(3,5-dimethyl-IH-pyrazol-4-yl)-5-{(5-hydroxymethyl)-3-methylisoxazol-4-yl)-l-methyl-IH-benzo[d]imidazoi--2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(3-methylpyridin-4-yl)-lH-benzo[d]imidazoi-2(3H)-one;
S-{S-(S,Dimethylisoxazol-4-yl)-l-methyl-7-{napthalen-1-yl)-1H-benzimidazol-2(3H)-one;
7-(3,5-dichloropyridin-4-yl)-5-{3,5-dimethylisoxazol-4-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-5-{1-methyl-2-oxo-2,3-dihydro-IH-benzo[d]imidazol-4-yl)-lH-benzo[d]imidazoi-2(3H)-one;
7-(2-chloro-5-methoxyphenyl)-5-{3,5-dimethylisoxazol-4-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-{3,5-dimethylisoxazol-4-yl)-l-methyl-7-{3-methylpyridin-4-yl)-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimet hyi isoxazol-4-yl)-7-(3,5-dimethylpyridin-4-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(o-toly)-lH-benzo[d]imidazoi-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-{2-fluoro-5-methoxyphenyl)-1-methyl-IH-benzo[d]imidazol-2(3H)-one;
7-(5-chloro-2-methoxyphenyl)-5-{3,5-dimethylisoxazol-4-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-{2-fluoro-3-methoxyphenyl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-{3,5-dimethylisoxazol-4-yl)-7-{2,4-dimethylthiazol-6-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-{3,5-dimethylisoxazol-4-yl)-7-{2,4-dimethylthiazol-6-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
5-{3,5-dimethylisoxazol-4-yl)-7-{2-methoxy-6-methylpyridin-3-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one;
7-{benzimidazol-5-yl)-5-{3,5-dimethylisoxazol-4-yl)-l-methyl-IH-benzo[d]imidazol-2(3H)-one; and
7-{cyclohex-1-en-l-yi)-5-{(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one,

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0121] Another aspect of the invention provides a method for inhibition of BET protein function by binding to bromodomains, and their use in the treatment and prevention of diseases and conditions in a mammal (e.g., a human) comprising administering a therapeutically effective amount of a compound of Formula I.


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interleukin-6 signaling suppresses not only Th17 but also interphotoreceptor retinoid binding protein -specific Thl by promoting regulatory T cells in experimental autoimmune uveoretinitis; "Invest Ophthalmol Vis Sci 52(6):3264-71 (2011)), and Vitiligo (Bassiouny, D.A. and Shaker, "Role of interleukin-17 in the pathogenesis of vitiligo," Clin Exp Dermatol 36(3):292-7 115. (2011)). Thus, the invention includes compounds of Formula I: stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof; pharmaceutical compositions comprising one or more of those compounds; and methods of using those compounds or compositions for treating these diseases.


[0124] In one embodiment, BET inhibitor compounds of Formula I, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used for treating rheumatoid arthritis (RA) and multiple sclerosis (MS). Strong proprietary data exist for the utility of BET inhibitors in preclinical models of RA and MS. R. Jahagirdar, S.M. et al., "An Orally Bioavailable Small Molecule RVX-297 Significantly Decreases Disease in a Mouse Model of Multiple Sclerosis," *World Congress of Inflammation*, Paris, France (2011). Both RA and MS are characterized by a dysregulation of the IL-6 and IL-17 inflammatory pathways (Kirmura, A. and T. Kishimoto, "IL-6: regulator of Treg/Th17 balance," *Curr Opin Immunol* 40(7):1630-5 (2010)) and thus would be especially sensitive to BET inhibition. In another embodiment, BET inhibitor compounds of Formula I may be used for treating sepsis and associated affictions. BET inhibition has been shown to inhibit development of sepsis, in part, by inhibiting IL-6 expression, in preclinical models in both published (Nicodemus, E., et al., "Suppression of inflammation by a synthetic histone mimic," *Nature* 468(7327):119-23 (2010)) and proprietary data.

[0125] In one embodiment, BET inhibitor compounds of Formula I, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat cancer. Cancers that have an overexpression, translocation, amplification, or rearrangement c-myc or other rnc family oncoproteins (MYCN, L-myc) are particularly sensitive to BET inhibition. Delmore, J.E., et al., "BET bromodomain inhibition as a therapeutic strategy to target c-Myc," *Cell* 146(6):904-17 (2010); Mertz, J.A., et al., "Targeting MYC dependence in cancer by inhibiting BET bromodomain," *Proc Natl Acad Sci USA* 108(40):16669-74 (2011). These cancers include, but are not limited to, B-acute lymphocytic leukemia, Burkitt's lymphoma, Diffuse large cell lymphoma, Multiple myeloma, Primary plasma cell leukemia, Atypical carcinoid lung cancer, Bladder cancer, Breast cancer, Cervix cancer, Colon cancer,


[0127] In one embodiment, because BET inhibitors decrease Brd-dependent recruitment of pTEFb to genes involved in cell proliferation, BET inhibitor compounds of Formula I, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat cancers that rely on pTEFb (Cdk9/cyclin T) and BET proteins to regulate oncogenes. These cancers include, but are not limited to, chronic lymphocytic leukemia and multiple myeloma (Tong, W.G., et al., "Phase I and pharmacologic study of SNS-032, a potent and selective Cdk2, 7, and 9 inhibitor, in patients with advanced chronic lymphocytic leukemia and multiple myeloma," *J Clin Oncol* 28(18):3015-22 (2010)), follicular lymphoma, diffuse large B-cell lymphoma with germinal center phenotype, Burkitt's lymphoma, Hodgkin's lymphoma, follicular lymphomas and activated, anaplastic large cell lymphoma (Belian, C., et al., "CDK9/CYCL1N T1 expression during normal lymphoid differentiation and malignant transformation," *J Pathol* 203(4):946-52 (2004)), neuroblastoma and primary neuroectodermal tumor (De Falco, G., et al., "Cdk9 regulates neural differentiation and its expression correlates with the differentiation grade of neuroblastoma and PNET tumors," *Cancer*...


[0129] Published and proprietary data have shown direct effects of BET inhibition on cell proliferation in various cancers, in one embodiment, BET inhibitor compounds of Formula I, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat cancers for which exist published and, for some, proprietary, in vivo and/or in vitro data showing a direct effect of BET inhibition on cell proliferation. These cancers include NMCL (NUT-midline carcinoma), acute myeloid leukemia (AML), acute B lymphoblastic leukemia (B-ALL), Burkitt's Lymphoma, B-cell Lymphoma, Melanoma, mixed lineage leukemia, multiple myeloma, pro-myelocytic leukemia (PMI), and non-Hodgkin's lymphoma. Filippakopoulos, P., et al., "Selective inhibition of BET bromodomains," Nature 468(7327): 1067-73 (2010); Dawson, M.A., et al., "inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia," Nature 478(7370) 529-33 (2011); Zuber, J., et al.,

[0130] In one embodiment, because of potential synergy or additive effects between BET inhibitors and other cancer therapy, BET inhibitor compounds of Formula 1 stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be combined with other therapies, chemotherapeutic agents, or anti-proliferative agents to treat human cancer and other proliferative disorders. The list of therapeutic agents which can be combined with BET inhibitors in cancer treatment includes, but is not limited to, ABT-737, Azacitidine (Vidaza), AZD1152 (Barasertib), AZD2281 (Olaparib), AZD6244 (Selumetinib), BEZ235, Bleomycin Sulfate, Bortezomib (Veicade), Busulfan (Myleran), Camptothecin, Cisplatin, Cyclophosphamide (Clafert), CYT387, Cytarabine (Ara-C), Dacarbazine, DAPT (GSS-IX), Decitabine, Dexamethasone, Doxorubicin (Adriamycin), Etoposide, Everolimus (RAD001), Flavopiridol (Alvocidib), Ganetespib (STA-9090), Gefitinib (Iressa), Idarubicin, Ifosfamide (Mitoxana), IFNa2a (Roferon A), Melphalan (Akeran), Methazolastone (temozolomide), Metformin, Mitoxantone (Novantrone), Paclitaxel, Phenformin, PKC412 (Midostaurin), PLX4032 (Vemurafenib), Pomalidomide (CC-4047), Prednisone (Deltasone), Rapamycin, Revlimid (Lenalidomide), Ruxolitinib (INCBO18424), Sorafenib (Nexavar), SU11248 (Sunitinib), 5U11274, Vinblastine, Vincristine (Oncovin), Vinorelbine (Navelbine), Vorinostat (SANA), and WP1130 (Degrasyn).

[0131] In one embodiment, BET inhibitor compounds of Formula 1 stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat benign proliferative and fibrotic disorders, including benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseuodotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, juvenile polyposis syndrome, idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, and cardiac fibrosis. Tang, X et al., "Assessment of Brd4 Inhibition in Idiopathic Pulmonary Fibrosis Lung Fibroblasts and in Vivo Models of Lung Fibrosis," Am J Pathology in press (2013).


In one embodiment, because of their ability to down-regulate viral promoters, BET inhibitor compounds of Formula I stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used as therapeutics for cancers that are associated with viruses including Epstein-Barr Virus (EBV), hepatitis virus (HBV, HCV), Kaposi’s sarcoma associated virus (KSHV), human papilloma virus (HPV), Merkei cell polyomavirus, and human cytomegalovirus (CMV). Gagnon, D., et al., "Proteasomal degradation of the papillomavirus E2 protein is inhibited by overexpression of bromodomain-containing protein..."

[0135] In one embodiment, because of the role of epigenetic processes and bromodomain-containing proteins in neurological disorders, BET inhibitor compounds of Formula I, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat diseases including, but not limited to, Alzheimer's disease, Parkinson's disease, Huntington disease, bipolar disorder, schizophrenia, Rubinstein-Taybi syndrome, and epilepsy. Prinjha, R.K., J. VVitherington, and K. Lee, "Place your BETs the therapeutic potential of bromodomains/" Trends Pharmacol Sci 33(3):146-53 (2012); Müller, S., et al., "Bromodomains as therapeutic targets," Expert Rev Mol Med 13:e29 (2011).


**Pharmaceutical Compositions**

[0137] Pharmaceutical compositions of the present disclosure comprise at least one compound of Formula I, or tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate.
thereof formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration. The most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used.

[0238] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of the present disclosure as powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association at least one compound of the present disclosure as the active compound and a carrier or excipient. (which may constitute one or more accessory ingredients). The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with at least one compound described herein as the active compound in a unit-dose formulation, for example, a tablet, which may contain from about 0.05% to about 95% by weight of the at least one active compound. Other pharmacologically active substances may also be present including other compounds. The formulations of the present disclosure may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components.

[0139] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by, for example, dissolving or dispersing, at least one active compound of the present disclosure as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. In general, suitable formulations may be prepared by uniformly and intimately admixing the at least one active-compound of the present disclosure with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or molding a powder or granules of at least one compound of the present disclosure, which may be optionally combined with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, at least one compound of the present disclosure in a free-flowing form, such as a powder or granules, which may be optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in
a suitable machine, where the powdered form of at least one compound of the present disclosure is moistened with an inert liquid diluent.

[0140] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising at least one compound of the present disclosure in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the at least one compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0141] Formulations of the present disclosure suitable for parenteral administration comprise sterile aqueous preparations of at least one compound of Formula I or tautomers, stereoisomers, pharmaceutically acceptable salts, and hydrates thereof, which are approximately isotonic with the blood of the intended recipient. These preparations are administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing at least one compound described herein with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the present disclosure may contain from about 0.1 to about 5% w/w of the active compound.

[0142] Formulations suitable for rectal administration are presented as unit-dose suppositories. These may be prepared by admixing at least one compound as described herein with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[0143] Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers and excipients which may be used include Vaseline, ianoine, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound (i.e., at least one compound of Formula I or tautomers, stereoisomers, pharmaceutically acceptable salts, and hydrates thereof) is generally present at a concentration of from about 0.1% to about 15% w/w of the composition, for example, from about 0.5 to about 2%.

[0144] The amount of active compound administered may be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician. For example, a dosing schedule may involve the daily or semi-daily administration of the encapsulated compound at a perceived dosage of about 1 μg to about 1000 mg. In another embodiment, intermittent administration, such as on a monthly or yearly basis, of a dose of the encapsulated compound may be employed. Encapsulation facilitates access to the site of action and allows the administration of the active ingredients simultaneously, in theory producing a synergistic effect. In accordance with standard dosing regimens, physicians will readily determine optimum dosages and will be able to readily modify administration to achieve such dosages.
A therapeutically effective amount of a compound or composition disclosed herein can be measured by the therapeutic effectiveness of the compound. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being used. In one embodiment, the therapeutically effective amount of a disclosed compound is sufficient to establish a maximal plasma concentration. Preliminary doses as, for example, determined according to animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices.

Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD$_{50}$ (the dose lethal to 50% of the population) and the ED$_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD$_{50}$/ED$_{50}$. Compositions that exhibit large therapeutic indices are preferable.

Data obtained from the cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. Therapeutically effective dosages achieved in one animal model may be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al., Cancer Chemother. Reports 50(4):219-244 (1966) and the following Table for Equivalent Surface Area Dosage Factors).

Equivalent Surface Area Dosage Factors:

<table>
<thead>
<tr>
<th>From:</th>
<th>Mouse (20 g)</th>
<th>Rat (150 g)</th>
<th>Monkey (3.5 kg)</th>
<th>Dog (8 kg)</th>
<th>Human (60 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>1</td>
<td>1/2</td>
<td>1/4</td>
<td>1/6</td>
<td>1/12</td>
</tr>
<tr>
<td>Rat</td>
<td>2</td>
<td>1</td>
<td>1/2</td>
<td>1/4</td>
<td>1/7</td>
</tr>
<tr>
<td>Monkey</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3/5</td>
<td>1/3</td>
</tr>
<tr>
<td>Dog</td>
<td>6</td>
<td>4</td>
<td>3/5</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>Human</td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED$_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Generally, a therapeutically effective amount may vary with the subject's age, condition, and gender, as well as...
the seventy of the medical condition in the subject. The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

[0149] In one embodiment, a compound of Formula I or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof, is administered in combination with another therapeutic agent. The other therapeutic agent can provide additive or synergistic value relative to the administration of a compound of the present disclosure alone. The therapeutic agent can be, for example, a statin; a PPAR agonist, e.g., a thiazolidinedione or fibrate; a niacin, a RVX, FXR or LXR agonist; a bile-acid reuptake inhibitor; a cholesterol absorption inhibitor; a cholesterol synthesis inhibitor; a choi esteryl ester transfer protein (CETP), an ion-exchange resin; an antioxidant; an inhibitor of AcylCoA cholesterol acyltransferase (ACAT) inhibitor; a tyrophostine; a sulfonylurea-based drug; a biguanide; an alpha-glucosidase inhibitor; an apolipoprotein E regulator; a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein; an LDL-lowering drug; an HDL-raising drug; an HDL enhancer; a regulator of the apolipoprotein A-IV and/or apolipoprotein genes; or any cardiovascular drug.

[0150] In another embodiment, a compound of Formula I or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof, is administered in combination with one or more anti-inflammatory agents. Anti-inflammatory agents can include immunosuppressants, TNF inhibitors, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and the like. Exemplary anti-inflammatory agents include, for example, prednisone; methyiprenisolone (Medrol®), triamcinolone, methotrexate (Rheumatrex®, Trexall®), hydroxychloroquine (Plaquenil®), sulfasalazine (Azulfidine®), leflunomide (Arava®), etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), rituximab (Rituxan®), abatacept (Orencia®), interleukin—1, anakinra (Kineret™), ibuprofen, ketoprofen, fenoprofen, naproxen, aspirin, acetaminophen, indomethacin, sulirsdac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodociac, mefenamic acid, meclofenamic acid, flufenamic acid, tolafenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxphenbutazone, difunisal, salsaialte, olsalazine, or sulfasalazine.

EXAMPLES

[0151] General Methods. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker AVANCE 300 spectrometer at 300 MHz or Bruker AVANCE 500 spectrometer at 500 MHz. Spectra are given in ppm (δ) and coupling constants, J values, are reported in hertz (Hz). Tetramethylsilane was used as an internal standard for 1H nuclear magnetic resonance. Mass spectra analyses were performed on Waters Aquity UPLC Mass Spectrometer in ESI or APCI mode.
when appropriate, Agilent 613GA Mass Spectrometer in ESI, APCI, or MultiMode mode when appropriate or Applied Biosystems API-150EX Spectrometer in ESI or APCI mode when appropriate.

Silica gel chromatography were in general performed on a Teledyne Isco CombiFlash® RF 200 system or a Teledyne Isco CombiFlash® Companion system.

Preparation of 4,6-bis[3,5-dimethylisoxazol-4-yl]-1H-benzo[d]imidazole-2(3H)-one (Example Compound 1).

![Chemical Structure](https://example.com/structure.png)

**Example 1**

**Step 1:** To a solution of 1 (5.0 g, 16.9 mmol) in ethanol (35 mL) was added iron (4.7 g, 84.5 mmol) and acetic acid (15 mL). The reaction was heated at 85 °C for an hour. The reaction mixture was cooled to room temperature, diluted with methanol (150 mL) and neutralized with sodium carbonate. The organic layer was dried over sodium sulfate, filtered and concentrated.

Purification by chromatography (silica gel, 0-20% ethyl acetate/hexanes) afforded 2 (3.15 g, 70%) as a brown solid: 1H NMR (300 MHz, DMSO-d$_6$) δ 6.77 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 5.17 (s, 2H), 4.77 (s, 2H).

**Step 2:** To a solution of 2 (3.15 g, 11.8 mmol) in 1,4-dioxane (50 mL) was added 1,1'-carbonyldimidazole (2.3 g, 14.2 mmol). The reaction was heated at 65 °C for 8 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification by chromatography (silica gel, 0-10% methanol/ethyl acetate) and further trituration with methanol afforded 3 (2.9 g, 83%) as a white solid: 1H NMR (300 MHz, DMSO-d$_6$) δ 11.26 (s, 1H), 11.08 (5, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.06 (d, j = 1.8 Hz, 1H).

**Step 3:** To a suspension of 3 (200 mg, 0.69 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (535 mg, 2.40 mmol), sodium carbonate (290 mg, 2.74 mmol) and tetrakis(triphenylphosphine)palladium (158 mg, 0.14 mmol). The reaction mixture was purged with nitrogen and was heated at 95 °C for 16 h. The mixture was diluted with methylene chloride (30 mL) and washed with brine (2 x 10 mL). The
organic layer was dried over sodium sulfate, filtered and concentrated. Purification by chromatography (silica gel, 0-100% ethyl acetate/hexanes) afforded Example Compound 1 (70 mg, 32%) as a white solid: \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 10.85 (s, 1H), 10.72 (s, 1H), 6.91 (s, 1H), 6.83 (d, \(J = 1.5\) Hz, 1H), 2.41 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H); ESI m/z 325 [M + H]+.

Preparation of 5,7-bis(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one (Example Compound 2).

[0155] Step 1: To a solution of 3 (400 mg, 1.37 mmol) in tetrahydrofuran (15 mL) was added di-tert-butyl dicarbonate (299 mg, 1.37 mmol) and potassium carbonate (189 mg, 1.37 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water and brine. The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to afford 4 (550 mg, >100%) as an off-white solid: \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.83 (s, 1H), 7.72 (s, 1H), 7.52 (d, \(J = 6.0\) Hz, 1H), 1.57 (s, 9H).

[0156] Step 2: To a solution of 4 (550 mg, 1.40 mmol) in tetrahydrofuran (10 mL) was added methyl iodide (0.12 mL, 1.96 mmol) and potassium carbonate (232 mg, 1.68 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with sat. sodium bicarbonate and brine. The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to afford 5 (550 mg, 96%) as an off-white solid: \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.89 (d, \(J = 1.8\) Hz, 1H), 7.63 (d, \(J = 1.8\) Hz, 1H), 3.56 (s, 3H), 1.58 (s, 9H).

[0157] Step 3: To a solution of 5 (550 mg, 1.40 mmol) in methylene chloride (10 mL) was added trifluoroacetic acid (3.40 mL) and the reaction was stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo, and the residue was then diluted with ethyl acetate (30 mL), and washed with sat. sodium bicarbonate and brine. The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to afford 6 (440 mg, >100%) as an off-white solid: \(^1\)H
NMR (300 MHz, DMSO- $d_6$) $\delta$ 11.37 (s, 1H), 7.32 (d, $J$ = 1.8 Hz, 1H), 7.11 (d, $J$ = 1.8 Hz, 1H), 3.53 (s, 3H).

[0158] Step 4: To a solution of 6 (430 mg, 1.41 mmol) in 1,4-dioxane (13 mL) and water (3 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (1.1 g, 4.92 mmol), sodium carbonate (598 mg, 5.64 mmol) and tetrakis(triphenylphosphine)palladium(0) (0) (163 mg, 0.14 mmol). The reaction mixture was purged with nitrogen and then heated at 95 °C for 16 h. The mixture was diluted with methylene chloride (50 mL) and washed with brine (2 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by chromatography (silica gel, 0-50% ethyl acetate/methylene chloride) afforded Example Compound 2 (220 mg, 46%) as a white solid: $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 11.17 (s, 1H), 7.01 (d, $J$ = 1.8 Hz, 1H), 6.79 (d, $J$ = 1.8 Hz, 1H), 2.95 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H), 2.10 (s, 3H); ESI m/z 339 [M + H]$^+$. Preparation of 5,7-bis[3,5-dimethylisoxazol-4-yl]benzo[i]oxazol-2(3H)-one (Example Compound 3).

[0159] Step 1: A solution of 7 (1.73 g, 6.48 mmol) and 1,1'-carbonyldiimidazole (2.63 g, 16.23 mmol) in 1,4-dioxane (60 mL) was refluxed for 16 h. After cooling to room temperature, the reaction mixture was mixed with silica gel (10 g) and concentrated. The resulting residue was purified by chromatography (silica gel, 0-50% ethyl acetate/heptane) to afford 8 (1.62 g, 85%) as a light brown solid: $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 12.16 (br s, 1 H), 7.53 (d, $J$ = 1.8 Hz, 1H), 7.29 (d, $J$ = 1.8 Hz, 1H); MM m/z 292 [M + H]$^+$.  

[0160] Step 2: A mixture of 8 (322 mg, 1.10 mmol), potassium (3,5-dimethylisoxazol-4-yl)trifluoroborate (782 mg, 3.85 mmol), potassium phosphate (1.05 g, 4.95 mmol) and tetrakis(triphenylphosphine)palladium(0) (153 mg, 0.13 mmol) in toluene (15 mL)/water (0.5 mL) was purged with nitrogen for 5 minutes. Then the reaction mixture was heated for 16 h at 90 °C. After cooling to room temperature, potassium (3,5-dimethylisoxazol-4-yl)trifluoroborate (220 mg, 1.08 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol), 1,4-dioxane (3 mL)/water (2 mL) were added. The reaction mixture was purged with nitrogen for two minutes, and then heated for 16 h at 90 °C. After cooling to room temperature, the reaction mixture was
concentrated. The resulting residue was purified by chromatography (silica gel, 0-50% ethyl acetate/heptane) followed by trituration with methylene chloride/hexanes to afford Example Compound 3 (45 mg, 13%) as a white solid: $^1$H NMR (300 MHz, DMSO- $d_6$) δ 11.90 (br s, 1H), 7.15-7.08 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); M M $m/z$ 324 [M + H]$^+$.

General Procedure A:

5-(3,5-dimethyl-1H-isoxazol-4-yl)-1-methyi -7-(2-methylpyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one (Example Compound 4),

[0161] Step 1: A solution of 9 (1.00 g, 4.61 mmol) in 1,4-dioxane (40 mL) and water (4 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborol3n-2-yl)isoxazole (1.23 g, 5.53 mmol), potassium carbonate (1.27 g, 9.22 mmol), and tetrakis(triphenylphosphine)palladium(0) (266 mg, 0.231 mmol). The reaction mixture was purged with nitrogen and heated at 90 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated and purified by chromatography (silica gel, 0-30% ethyl acetate/hexanes) to give 10 (950 mg, 88%) as a yellow solid: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, $J = 2.1$ Hz, 1H), 7.26 (dd, $J = 2.1$ Hz, 8.5 Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 1H), 6.14 (s, 2H), 2.40 (s, 3H), 2.26 (s, 3H); ESI $m/z$ 234 [M + H]$^+$.

[0162] Step 2: A solution of 10 (940 mg, 4.03 mmol) in acetic acid (15 mL) at 0 °C was added W-bromosuccinimide (753 mg, 4.23 mmol). The reaction was warmed to room temperature and stirred for 16 h. The mixture was concentrated in vacuo. The residue was suspended in hot MeOH, cooled to room temperature and was basified with 10% aq. NaHCO$_3$. The mixture was diluted with water and filtered. The solid was washed with water and dried in vacuo to afford 11 (1.10 g, 87%) as a yellow solid: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 (d, $J = 2.1$ Hz, 1H), 7.61 (d, $J = 2.1$ Hz, 1H), 6.69 (br s, 2H), 2.40 (s, 3H), 2.25 (s, 3H); ESI $m/z$ 312 [M + H]$^+$.

[0163] Step 3: A solution of 11 (1.00 g, 3.21 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil, 141 mg, 3.53 mmol) at room temperature under nitrogen. The mixture was stirred at room temperature for 30 min and iodomethane (410 mg, 2.98 mmol) was
added. The reaction mixture was stirred at room temperature for 16 h. \(\text{NH}_4\text{Cl/H}_2\text{O} (10 \text{ mL})\) was added, the mixture was stirred for 30 min, concentrated and purified by chromatography (silica gel, 0-25% ethyl acetate/hexanes) to give 12 (370 mg, 35%) as an orange solid. \(^1\text{H} \text{NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta\):

- 7.75 (d, \(J = 2.1 \text{ Hz}, 1\text{H}\)), 7.57 (d, \(J = 2.1 \text{ Hz}, 1\text{H}\)), 6.25 (q, \(J = 5.6 \text{ Hz}, 1\text{H}\)), 3.06 (d, \(J = 5.5 \text{ Hz}, 3\text{H}\)), 2.40 (s, 3H), 2.26 (s, 3H); ESI m/z 335 [M + H]^+.

[0164] Step 4: To a solution of 12 (2.43 g, 7.45 mmol) in tetrahydrofuran (40 mL) was added sodium dithionite (7.78 g, 44.7 mmol) in water (40 mL). The reaction mixture was stirred at room temperature for 2 h and concentrated under vacuum. To the residue was added 2N HCl (30 mL), the mixture was heated to reflux for 1 min, and concentrated under vacuum. The residue was dissolved in MeOH, adjusted to pH 8 by saturated NaHCO\(_3\) (10% in water) and concentrated under vacuum. The residue was purified by chromatography (silica gel, 0-100% ethyl acetate/hexanes) to afford 13 (1.92 g, 87%) as a yellow solid. \(^1\text{H} \text{NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta\):

- 6.79 (d, \(J = 1.8 \text{ Hz}, 1\text{H}\)), 6.50 (d, \(J = 1.8 \text{ Hz}, 1\text{H}\)), 4.08 (br.s, 2H), 3.29 (br.s, 1H), 2.71 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H); ESI m/z 296 [M + H]^+.

[0165] Step 5: To a mixture of 13 (1.92 g, 6.49 mmol) in 1,4-dioxane (50 mL) was added 1,1'-carbonyldimidazole (2.10 g, 12.9 mmol) and DMAP (10 mg). The reaction was heated in a sealed tube at 100 °C for 16 h. The mixture was concentrated and purified by chromatography (silica gel, 0-100% ethyl acetate in hexanes) to afford 14 (2.03 g, 97%) as a yellow solid. \(^1\text{H} \text{NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta\):

- 7.08 (d, \(J = 1.4 \text{ Hz}, 1\text{H}\)), 6.89 (d, \(J = 1.4 \text{ Hz}, 1\text{H}\)), 3.78 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H); ESI m/z 322 [M + H]^+.

[0166] Step 6: To a solution of 14 (100 mg, 0.31 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (88 mg, 0.40 mmol), sodium carbonate (66 mg, 0.62 mmol) and tetrakis(triphenylphosphine)palladium (0) (18 mg, 0.016 mmol). The reaction mixture was purged with nitrogen and then heated at 95 °C for 16 h. The mixture was diluted with methylene chloride (50 mL) and washed with brine (2 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by chromatography (silica gel, 0-5% methanol/methylene chloride) afforded Example Compound 4 (55 mg, 53%) as a white solid. \(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{DMSO-}d_6) \delta\):

- 11.17 (s, 1H), 8.54 (dd, \(J = 5.0, 1.7 \text{ Hz}, 1\text{H}\)), 7.74 (dd, \(J = 7.6, 1.8 \text{ Hz}, 1\text{H}\)), 7.36-7.29 (m, 1H), 7.00 (d, \(J = 1.8 \text{ Hz}, 1\text{H}\)), 6.78 (d, \(J = 1.5 \text{ Hz}, 1\text{H}\)), 2.70 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H); ESI m/z 335 [M + H]^+.
Preparation of 6-(3,5-dimethylisoxazol-4-yl)-4-(13,5-trimethylhydrazino-4-yl)-1\textsubscript{H}-pyrazole (Example Compound 22).

![Chemical Structure](image)

**Step 1:** To a mixture of 11 (500 mg, 1.6 mmol), 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1\textsubscript{H}-pyrazole (454 mg, 1.92 mmol), potassium carbonate (443 mg, 3.20 mmol), water (2 mL) and 1,4-dioxane (9 mL) was added tetrakis(triphenylphosphine)palladium(0) (93 mg, 0.08 mmol). The suspension was heated at 90 °C for 17 h. After cooling to room temperature, methanol (20 mL) and silica gel (10 g) were added. The mixture was concentrated to dryness and the resulting powder was purified by flash chromatography (silica gel, 0-90% ethyl acetate/hexanes) affording 15 as a yellow solid (291 mg, 53%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta 8.05 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.25 (br s, 2H), 3.82 (s, 3H), 2.43 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H).

**Step 2:** To a solution of 15 (290 mg, 0.85 mmol) in THF (20 mL) was added a solution of sodium dithionite (887 mg, 5.10 mmol) in water (20 mL). The solution stirred at room temperature for 17 h. The reaction was concentrated to dryness and methanol (30 mL) was added. The suspension stirred at room temperature for 3 h and was filtered. The filtrate was concentrated to dryness and a solution of 2N aq. HCl (20 mL) was added. The solution was brought to reflux for 5 minutes and then cooled to room temperature. The solvent was removed under reduced pressure and silica gel (10 g) and methanol (20 mL) were added. The methanol was removed and the adsorbed silica mixture was subject to flash chromatography (silica gel, 0-50% CMA (CMA: 80% CH\textsubscript{3}Cl, 18% methanol, 2% NH\textsubscript{4}OH) in CH\textsubscript{2}Cl\textsubscript{2}) affording 16 as a light brown solid (201 mg, 76%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta 6.59 (d, J = 2.0 Hz, 1H), 6.44 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H), 3.48 (br s, 4H), 2.39 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H).
Step 3: To a solution of 16 (200 mg, 0.64 mmol) in anhydrous 1,4-dioxane (10 mL) at room temperature was added 1,1'-carbonyldiimidazole (125 mg, 0.77 mmol). The mixture was heated at 65 °C for 17 h and then cooled to room temperature. After adding silica gel (10 g) and concentrating the mixture to dryness, the material was subject to flash chromatography (silica gel, 0-10% methanol in CH₂Cl₂) and the product fractions were concentrated to an off-white solid. The solid was triturated with ethyl acetate (20 mL) and the suspension was filtered. The solid collected was dried in a vacuum oven for 17 h affording the product Example Compound 22 (197 mg, 91%) as an off-white solid: ¹H NMR (500 MHz, DMSO-d₆) δ 10.7 (s, 1H), 10.4 (s, 1H), 6.82 (d, J = 1.5 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 3.70 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H); ESI m/z 338 [M + H].

General Procedure B:
Preparation of 5-{3,5-dimethylisoxazol-4-yl}-1-methyl-7-{1(3,5-trimethyl-1H-pyrazol-4-yl)amino}-1H-benzo[d]imidazo[2(3H)-one (Example Compound 26).

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Step 1: To a solution of 14 (2.03 g, 6.30 mmol) in dichloromethane (100 mL) was added triethylamine (2.63 mL, 18.9 mmol) followed by triethyl chloride (5.27 g, 18.9 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated, the residue was purified by chromatography (silica gel, 0-20% ethyl acetate/hexanes) to give 17 (1.55 g, 44%) as an off-white solid: ¹H NMR (500 MHz, CD₂OD) δ 7.50-7.15 (m, 15H), 7.10 (d, J = 1.3 Hz, 1H), 6.16 (d, J = 1.3 Hz, 1H), 3.72 (s, 3H), 2.15 (s, 3H), 1.96 (s, 3H); ESI m/z 564 [M + H].

Step 2: To a solution of 17 (200 mg, 0.355 mmol) in toluene (10 mL) under nitrogen atmosphere was added 1,3,5-trimethyl-1H-pyrazol-4-amine (66 mg, 0.53 mmol), cesium
carbonate (231 mg, 0.710 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1',1'-bipheoyl (25 mg, 0.053 mmol), and tris(dibenzylideneacetone) dipalladium(O) (33 mg, 0.036 mmol). The reaction mixture was heated at 90 °C overnight, cooled to room temperature, and purified by chromatography (silica gel, 0-100% ethyl acetate/hexanes) to give 1S (140 mg, 67%) as a yellow solid. 1H NMR (500 MHz, CD3OD) δ 7.47 (d, J = 7.3 Hz, 6H), 7.24 (t, J = 6.5 Hz, 6H), 7.18 (t, J = 6.5 Hz, 3H), 6.28 (s, IH), 5.85 (d, J = 1.3 Hz, IH), 5.65 (d, J = 1.3 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.84 (s, 3H).

[0172] Step 3: A mixture of 18 (140 mg, 0.236 mmol) and TFA (2 mL) were stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. The residue was dissolved in MeOH and basified using concentrated NH4OH. The mixture was concentrated under vacuum and purified by reverse phase HPLC on Polaris C18 column eluted with 10-90% CH3CN in H2O to give Example Compound 26 (24 mg, 28%) as an off-white solid. 1H NMR (500 MHz, CD3OD) δ 5.45 (s, IH), 5.89 (s, IH), 3.77 (s, 3H), 3.72 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H); ESI m/z 367 [M + H]+.

Preparation of 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-methylpyridin-3-yl)oxy)-1H-benzo[d]imidazol-2(3H)-one (Example Compound 31).

[0173] Step 1: To a solution of 17 (200 mg, 0.355 mmol) in DMSO (10 mL) under nitrogen atmosphere was added 2-methylpyridin-3-ol (58 mg, 0.53 mmol), K2PO4 (188 mg, 0.888 mmol), picolinic acid (9 mg, 0.07 mmol), and CuI (7 mg, 0.04 mmol). The reaction mixture was heated at 90 °C overnight, cooled to room temperature, and concentrated under vacuum. The residue was purified by chromatography (silica gel, 0-100% ethyl acetate/hexanes) to give 19 (130 mg, 62%) as a yellow solid. 1H NMR (500 MHz, CDCl3) δ 8.30 (d, J = 1.5, 4.5 Hz, 1H), 7.46 (d, J = 7.4 Hz, 6H), 7.33-7.20 (m, 9H), 7.18-7.10 (m, 2H), 6.24 (d, J = 1.3 Hz, IH), 5.55 (d, J = 1.3 Hz, IH), 3.51 (s, 3H), 2.58 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H); ESI m/z 593 [M + H]+.

[0174] Step 2: A mixture of 19 (130 mg, 0.220 mmol) and TFA (2 mL) were stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. The residue was dissolved in MeOH and basified with concentrated NH4OH. The mixture was concentrated under vacuum and purified by reverse phase HPLC on a Polaris C18 column eluted with 10-90% CH3CN in...
H;0 to give Example Compound 31 (35 mg, 46%) as an off-white solid; \[^{1}\text{H} \text{NMR (500 MHz, CD}_{3}\text{OD)} \delta 8.21 (dd, J = 1.5, 4.6 Hz, 1H), 7.31 (dd, J = 1.5, 8.3 Hz, 1H), 7.27 (dd, J = 4.6, 8.4 Hz, 1H), 6.87 (d, J = 1.4 Hz, 1H), 6.49 (d, J = 1.4 Hz, 1H), 3.51 (s, 3H), 2.59 (s, 3H), 2.34 (s, 3H), 2.17 (s, 3H); ESI \text{m/z} 351 [\text{M}+H]^+.

General Procedure C:

5-(5-(hydroxymethyl)-3-methylisoxazol-4-yl)-1-methyl-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-benz[d]isoxazol-2(3H)-one (Example Compound 28).

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\begin{align*}
\text{Step 1: To a solution of 20 (3.20 g, 28.32 mmol) in AcOH (5 mL) was added } & \text{N-bromosuccinimide (6.05 g, 33.98 mmol) and } \text{H}_2\text{SO}_4 (0.1 mL). The reaction mixture was heated to 120} \text{°C for 3 h. The reaction mixture was concentrated, the residue was dissolved in EtOAc (200 mL), washed with saturated } \text{NaHCO}_3 (100 mL), \text{saturated } \text{Na}_2\text{S}_2\text{O}_3 (3 \times 50 mL) \text{ and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give 21 (5.50 g, 83%) as a pale yellow solid; } \[^{1}\text{H} \text{NMR (300 MHz, CDCl}_3) \delta 5.16 (s, 2H), 2.31 (s, 3H), 2.13 (s, 3H).}
\end{align*}
\]

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\text{Step 2: To a solution of 22 (10.0 g, 37.9 mmol) in DMSO (100 mL) at 0 °C was added } \text{NaH (60%, 1.97 g, 49.3 mmol). The mixture was stirred at 0 °C for 30 minutes, } \text{CH}_3\text{I (3.54 mL, 56.9 mol) was added dropwise, the mixture was stirred at 0 °C for 1 h, then warmed to room temperature and stirred overnight. The reaction was quenched with saturated } \text{NH}_4\text{Cl (100 mL)} \text{ and extracted with EtOAc (3 x 150 mL). The combined organic layer was washed with brine (3 x 150 mL), dried over sodium sulfate, filtered and concentrated. The residue was triturated with EtOAc/hexanes to afford}
\]

52
23 (8.5 g, 80%) as an orange solid: $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.39 (q, $J = 5.1$ Hz, 1H), 8.35 (d, $J = 1.2$ Hz, 1H), 7.72 (dd, $J = 8.7$, 0.9 Hz, 1H), 6.98 (d, $J = 9.7$ Hz, 1H), 2.97 (d, $J = 4.8$ Hz, 3H), 1.29 (s, 12H).

[0177]  Step 3: A mixture of 21 (2.34 g, 10.0 mmol), 23 (4.0 g, 14.4 mmol) and potassium carbonate (4.14 g, 30.0 mmol) in 1,4-dioxane (60 mL) and water (10 mL) was purged with nitrogen for 10 minutes. PdCl$_2$(dpff) (817 mg, 1.0 mmol) was then added. The reaction mixture was heated at 90 °C for 7 h, diluted with EtOAc (300 mL), washed with brine (2 x 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (silica gel, 10-50% ethyl acetate/hexanes) to afford 24 (1.15 g, 37%) as an orange gum: $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.30 (q, $J = 5.1$ Hz, 1H), 8.08 (d, $J = 2.1$ Hz, 1H), 7.62 (dd, $J = 9.0$, 1.8 Hz, 1H), 7.11 (d, $J = 9.0$ Hz, 1H), 5.14 (s, 2H), 3.00 (d, $J = 4.8$ Hz, 3H), 2.26 (s, 3H), 2.05 (s, 3H).

[0178]  Step 4: A solution of 24 (1.15 g, 3.77 mmol) in CH$_3$CN (50 mL) was cooled to 0 °C and N-bromosuccinimide (1.21 g, 6.79 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to rt for 3 h. The reaction mixture was diluted with EtOAc (200 mL), then washed with saturated Na$_2$S$_2$O$_3$ (3 x 50 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was suspended in EtOAc/hexanes (1/1, 100 mL), sonicated and filtered, and the filtrate was concentrated to give 25 (1.31 g, 90%) as an orange solid: $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.87 (d, $J = 2.1$ Hz, 1H), 7.81 (d, $J = 2.1$ Hz, 1H), 6.55 (q, $J = 5.1$ Hz, 1H), 5.15 (s, 2H), 2.73 (d, $J = 5.4$ Hz, 3H), 2.25 (s, 3H), 2.03 (s, 3H).

[0179]  Step 5: A mixture of 25 (95 mg, 0.243 mmol), 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (115 mg, 0.486 mmol) and Na$_2$CO$_3$ (77 mg, 0.729 mmol) in 1,4-dioxane (5 mL) and water (0.4 mL) was purged with nitrogen for 5 minutes, PdCl(PPh$_3$)$_4$ (28 mg, 0.024 mmol) was added and the reaction mixture was heated at 90 °C for 18 h. The reaction mixture was diluted with EtOAc (30 mL), filtered and concentrated. The residue was purified by chromatography (silica gel, 0-5% methanol/ethyl acetate) to afford 26 (38 mg, 38%) as an orange oil: $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.91 (d, $J = 2.4$ Hz, 1H), 7.26 (d, $J = 2.4$ Hz, 1H), 6.99 (q, $J = 5.4$ Hz, 1H), 5.17 (s, 2H), 3.71 (s, 3H), 2.45 (d, $J = 5.4$ Hz, 3H), 2.28 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H).

[0180]  Step 6: To a solution of 26 (38 mg, 0.092 mmol) in tetrahydrofuran (5 mL) and water (4 mL) was added sodium dithionite (104 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 4 h, 2 N HCl (1 mL) was added, the mixture was heated to reflux for 15 minutes then cooled to rt, Na$_2$CO$_3$ was added slowly to adjust to pH 9. The mixture was extracted with CH$_2$Cl$_2$ (50 mL), the organic layer was washed with brine (30 mL), filtered and concentrated. The residue was dissolved in 1,4-dioxane (2 mL), 1,1'-carbonyldimidazole (19 mg, 0.12 mmol) was added and the mixture was heated to 100 °C for 18 h. The mixture was concentrated, the residue
was dissolved in THF (3 mL), NaOH (1 N in water, 0.5 mL) was added and the reaction mixture was heated to 50 °C for 2 h. The mixture was diluted with EtOAc (15 mL), washed with brine (3 x 10 mL), and the organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (silica gel, 0-10% methanol/ethyl acetate) followed by trituration with EtOAc/hexanes to afford Example Compound 28 (9 mg, 24%) as an off-white solid: \( ^1H \text{NMR} (300 \text{ MHz}, \text{DMSO-}d_6) \delta 11.08 (s, 1H), 7.03 (d, J = 1.5 \text{ Hz}, 1H), 6.74 (d, J = 1.8 \text{ Hz}, 1H), 5.65 (t, J = 5.7 \text{ Hz}, 1H), 4.49 (d, J = 5.7 \text{ Hz}, 2H), 3.73 (s, 3H), 2.88 (s, 3H), 2.27 (s, 3H), 2.09 (s, 3H); \text{ESI m/z} 368 [M + H]+.

Preparation of 4,6-bis(3,5-dimethylisoxazol-4-yl)-1\(^3\)-dimethyl-1H-benzo[d]imidazol-2(3H)-one (Example Compound 15).

[Q181] Step 1: To a solution of 3 (300 mg, 1.03 mmol) in tetrahydrofuran (6 mL) was added methyl iodide (0.16 mL, 2.57 mmol) and potassium carbonate (284 mg, 2.06 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with sat. sodium bicarbonate and brine. The organic layer was separated, dried over sodium sulfate and concentrated. The residue was triturated with EtOAc to afford 27 (150 mg, 46%) as an off-white solid: \text{ESI m/z} 320 [(M+2) + H].

[Q182] Step 2: To a solution of 27 (150 mg, 0.47 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (366 mg, 1.64 mmol), sodium carbonate (198 mg, 1.88 mmol) and tetrakis(triphenylphosphine)palladium (0) (27 mg, 0.024 mmol). The reaction mixture was purged with nitrogen and then heated at 95 °C for 16 h. The mixture was diluted with methylene chloride (50 mL) and washed with brine (2 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by chromatography (silica gel, 0-50% ethyl acetate/methylene chloride) afforded Example Compound 15 (48 mg, 29%) as a white solid: \( ^1H \text{NMR} (300 \text{ MHz}, \text{DMSO-}d_6) \delta 7.26 (d, J = 1.8 \text{ Hz}, 1H), 6.84 (d, J = 1.8 \text{ Hz}, 1H), 3.40 (s, 3H), 3.00 (s, 3H), 2.43 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 2.09 (s, 3H); \text{ESI m/z} 353 [M + H].
General Procedure D: Preparation of 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(3-methylpyridin-4-yl)-1H-benzo[d]imidazole-2(3H)-one (Example Compound 38),

[0183] Step 1: To a solution of 17 (500 mg, 0.887 mmol) in 1,4-dioxane (10 mL) was added 4,4',4,5,5',5'-octamethyl-2,2'-b[i(l,3,2'-dioxaborolane) (338 mg, 1.33 mmol), potassium acetate (174 mg, 1.77 mmol), and [1,1'-bis(diphenyolphosphino)ferrocene] dichloropalladium(0) (65 mg, 0.089 mmol). The reaction mixture was purged with nitrogen for 5 minutes and then heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated and purified by chromatography (silica gel, 0-50% ethyl acetate in hexanes) to afford 28 (310 mg, 57%) as a yellow solid: 1H NMR (500 MHz, CD3OD) δ 7.50-7.40 (m, 6H), 7.30-7.18 (m, 10H), 6.27 (d, J = 1.6 Hz, 1H), 3.51 (s, 3H), 2.13 (s, 3H), 1.95 (s, 3H), 1.39 (s, 12H); ESI m/z 612 [M + H]+.

[0184] Step 2: To a solution of 28 (100 mg, 0.164 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added 4-bromo-3-methylpyridine (57 mg, 0.33 mmol), potassium bicarbonate (68 mg, 0.49 mmol), and tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.003 mmol). The reaction mixture was purged with nitrogen for 5 minutes and then heated at 90 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was dissolved in TFA (2 mL) and stirred at room temperature for 2 h. The mixture was concentrated. The residue was purified by chromatography (silica gel, 0-20% methanol/ethyl acetate). The product was further purified by reverse phase HPLC on a Polaris C18 column eluting with 10-90% CH3CN in H2O to give Example Compound 38 (28 mg, 51%) as an off-white solid: 1H NMR (500 MHz, CD3OD) δ 8.53 (s, 1H), 8.47 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 5.0 Hz, 1H), 7.09 (d, J = 1.4 Hz, 1H), 6.79 (d, J = 1.4 Hz, 1H), 2.88 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H); ESI m/z 335 [M + H]+.
General Procedure E:
Preparation of 3-(6-(3-S-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazo[4-yl]-4-methylbenzamide (Example Compound 29).

Example 16

Example 29

[0185] To a solution of Example 16 (35 mg, 0.10 mmol) in ethanol (2 mL) was added 2 N NaOH (0.49 mL). The reaction mixture was heated to 85 °C for 2 h. The reaction mixture was diluted in methylene chloride (70 mL), washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography (silica gel, 0-10% methanol/methylene chloride) to afford Example 29 (34 mg, 92%) as white solid: 1H NMR (500 MHz, DMSO-d6) δ 11.11 (br.s, 1H), 7.94 (br.s, 1H), 7.87 (dd, J = 7.8, 2.0 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.31 (br.s, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.2 (s, 3H), 2.15 (s, 3H); ESI m/z 377 [M + H]+.

Preparation of 6-(3-S-dimethylisoxazol-4-yl)-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1W benzo[d3imidazole-2(3H)-thione (Example 23).

Example 22

Example 23

[0186] Lawesson’s reagent (0.485 g, 1.20 mmol) was added to a solution of Example Compound 22 (0.337 g, 1.00 mmol) in 1,4-dioxane (2 mL). The reaction was stirred at 180 °C for 6 h under microwave heating conditions. The reaction was cooled to rt, concentrated under reduced pressure and quenched with water (75 mL). The resulting precipitate was collected by filtration, washed with water, then ethyl acetate (20 mL) and dried under vacuum. The residue was purified by flash column chromatography (silica gel, 0-5% methanol/dichloromethane) followed by prep. HPLC to afford Example 23 (0.066 g, 19%) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ 12.37 (br s,
2H), 7.01 (s, 1H), 6.87 (s, 1H), 3.71 (s, 3H), 2.42 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H); ESI MS \( m/z \) 352 \( [M-H]^+ \).

Preparation of 6-(3,5-dimethylisoxazol-4-yl)-4-(4-methylpyridin-3-yl)-1H-benzo[d]imidazole-2(3H)-thione (Example Compound 24).

[0187] Step 1: To a degassed solution of 11 (6.24 g, 20 mmol), 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)pyridine (6.57 g, 30 mmol) and K\(_2\)P\(_{10}\) (12.74 g, 60 mmol) in 1,4-dioxane (126 mL) and water (12.6 mL) was added Pd(PPh\(_3\))\(_4\) (2.31 g, 2 mmol). The reaction was heated at 100 °C for 20 h under \( \text{N}_2 \). The reaction was cooled to \( \text{rt} \), dried over MgSO\(_4\), filtered through silica gel and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 80% \( \text{CH}_3\text{Cl}_2/\text{ethyl acetate} \) to give an impure mixture that was dissolved in ethyl acetate (200 mL) and extracted with 2N HCl (22 mL) and water (4 x 20 mL). The combined aqueous extracts were washed with diethyl ether (2 x 50 mL) and basified with solid K\(_2\)CO\(_3\) (about 7.3 g) to pH 9. The aqueous was extracted with chloroform (4 x 20 mL). The combined organics were dried over MgSO\(_4\), filtered and concentrated under reduced pressure to give 29 (4.48 g, 60%) as an orange solid: \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.61 (d, \( J = 5.2 \) Hz, 1H), 8.46 (s, 1H), 8.14 (d, \( J = 2.0 \) Hz, 1H), 7.33 (d, \( J = 5.2 \) Hz, 1H), 7.16 (d, \( J = 2.0 \) Hz, 1H), 6.06 (br.s, 2H), 2.44 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H).

[0188] Step 2: Concentrated hydrochloric acid (20.7 mL, 249 mmol) was added in one portion to a stirred suspension of 29 (4.48 g, 13.8 mmol) and tin granules (4.92 g, 41.4 mmol) in ethanols (146 mL). The reaction was stirred at \( \text{rt} \) for 23 h. After that time the resulting precipitate was collected by filtration, washed with ethanol (2 x 50 mL), then \( \text{B}_2\text{O}_3 \) (2 x 100 mL) and dried under vacuum. The material was dissolved in water (100 mL) and the pH of the resulting solution was
adjusted to 9 with solid K₂CO₃ (4.9 g). The aqueous solution was extracted with chloroform (6 x 20 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to 30 (3.27 g, 80%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, J = 5.2 Hz, 1H), 8.46 (s, 1H), 7.26 (d, J = 5.2 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 2.0 Hz, 1H), 3.54 (br.s, 2H), 3.31 (br s, 2H), 2.40 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H).

[0189] Step 3: 1,1'-thiocarbonyldiimidazole (0.267 g, 1.5 mmol) was added in one portion to a stirred suspension of 30 (0.294 g, 1.0 mmol) in anhydrous THF (10 mL). The reaction was heated at reflux with stirring for 21 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL), washed with water (3 x 10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 0-2% methanol/chloroform) to give Example 2 Compound 4 (0.305 g, 91%) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 12.58 (hr.s, 1H), 11.33 (br.s, 1H), 8.45 (s, 1H), 8.23 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 1.2 Hz, 1H), 6.91 (d, J = 1.2 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H); ESI MS m/z 337 [M + Hf].

Preparation of 3-(6-(3,5-dimethylisoxazol-1-4-yl)-2-thioxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-4-methylbenzonitrile (Example Compound 25).

[0190] Starting with (5-cyano-2-methylphenyl)boronic acid, compound 31 was prepared using the method for Example Compound 22 step 1 to 2.

[0191] A mixture of 31 (0.2 g, 0.63 mmol) and 1,1'-thiocarbonyldiimidazole (0.17 g, 0.95 mmol) in THF (8.0 mL) was heated at reflux for 18 h. The reaction was cooled to rt, filtered and concentrated under reduced pressure, ice-cold water (20 mL) was added to the residue and the product was extracted with chloroform (2 x 20 mL). The combined organics were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 0-3% MeOH/dichloromethane) to give Example Compound 25 (0.19 g, 83.9%) as an off-white solid: ¹H NMR (400 MHz, CDCl₃) δ 10.26 (br.s, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 2.43 (s, 3H), 2.29 (s, 6H); ESI MS m/z 361 [M + Hf].
Tataie 1. Examples prepared using methods described above.

<table>
<thead>
<tr>
<th>Example Compound</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>General procedure</th>
<th>Characterization</th>
<th>Purity HPLC</th>
</tr>
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<tr>
<td>1</td>
<td>4,6-bis(3,5-dimethylisoxa zol-4-yl)-1H-benzo[d]imidazo<a href="3H">2</a>-one</td>
<td>[Structure Image]</td>
<td>none</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.85 (s, 1H), 10.72 (s, 1H), 6.91 (s, 1H), 6.83 (d, J = 1.5 Hz, 1H), 2.41 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H); ESI m/z 325 [M + H]$^+$.</td>
<td>98.3</td>
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<tr>
<td>2</td>
<td>5,7-bis(3,5-dimethylisoxa zol-4-yl)-1-methyl-1H-benzo[d]imidazo<a href="3H">2</a>-one</td>
<td>[Structure Image]</td>
<td>none</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.17 (s, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 2.95 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H), 2.10 (s, 3H); ESI m/z 339 [M + H]$^+$.</td>
<td>&gt;99</td>
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<tr>
<td>3</td>
<td>5,7-bis(3,5-dimethylisoxa zol-4-yl)benzoxazolo<a href="3H">2</a>-one</td>
<td>[Structure Image]</td>
<td>none</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.90 (br s, 1H), 7.15–7.08 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); MM m/z 324 [M – H]$^-$.</td>
<td>&gt;99</td>
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<td>4</td>
<td>5-(3,5-dimethylisosoxa zol-4-yl)-1-methyl-7-(2-methylpyridin-3-yl)-1H-benzo[d]imidazo<a href="3H">2</a>-one</td>
<td>[Structure Image]</td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.17 (s, 1H), 8.54 (dd, J = 5.0, 1.7 Hz, 1H), 7.74 (dd, J = 7.6, 1.8 Hz, 1H), 7.36-7.29 (m, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 2.70 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H); ESI m/z 335 [M + H]$^+$.</td>
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<td>5</td>
<td>5-(3,5-dimethylisoxa zol-4-yl)-1-methyl-7-(2-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure Diagram" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.17 (s, 1H), 7.93-7.87 (m, 1H), 7.79-7.66 (m, 2H), 7.64-7.57 (m, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.79-6.76 (m, 1H), 2.62 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H); ESI m/z 388 [M + H]$^+$.</td>
<td>98.3</td>
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<td>6</td>
<td>5-(3,5-dimethylisoxa zol-4-yl)-1-methyl-7-[4-methylpyridin-3-yl]-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure Diagram" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.17 (s, 1H), 8.54-8.47 (m, 2H), 7.39 (d, J = 4.8 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 2.70 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H), 2.14 (s, 3H); ESI m/z 335 [M + H]$^+$.</td>
<td>&gt;99</td>
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<tr>
<td>7</td>
<td>7-(1,3-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxa zol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure Diagram" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.06 (s, 1H), 7.76 (s, 1H), 6.92 (d, J = 1.5 Hz, 1H), 6.71 (d, J = 1.8 Hz, 1H), 3.82 (s, 3H), 2.95 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H); ESI m/z 338 [M + H]$^+$.</td>
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<td>8</td>
<td>5-(3,5-dimethylisoxa zol-4-yl)-1-methyl-7-(2-(trifluoromethyl)pyridin-3-yl)-1H-benzo[d]imidazol-</td>
<td><img src="image" alt="Structure Diagram" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.29 (s, 1H), 8.86 (d, J = 5.3 Hz, 1H), 8.10-8.07 (m, 1H), 7.91-7.87 (m, 1H), 7.08 (d, J = 1.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 2.87 (s, 3H), 2.49 (s, 3H), 2.22</td>
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<tr>
<td>9</td>
<td>5-(3,5- dimethylisoxa zol-4-yl)-1- methyl-7- (1,3,5-tri methyl-1H-pyrazol-4-yl)- 1H-benzo [d]imidazol-2(3H)-one</td>
<td><img src="image1" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.05 (s, 1H), 6.93 (d, $J = 1.7$ Hz, 1H), 6.65 (d, $J = 1.7$ Hz, 1H), 3.72 (s, 3H), 2.88 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H); ESI m/z 352 [M + H]+.</td>
<td>&gt;99</td>
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<td>10</td>
<td>5-(3,5- dimethylisoxa zol-4-yl)-1- methyl-7-(4- methylisothiaz ol-5-yl)-1H- benzo[d]imid azol-2(3H)-one</td>
<td><img src="image2" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.23 (s, 1H), 9.15 (s, 1H), 7.03 (d, $J = 1.7$ Hz, 1H), 6.86 (d, $J = 1.7$ Hz, 1H), 2.98 (s, 3H), 2.40 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H); ESI m/z 341 [M + H]+.</td>
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<td>11</td>
<td>5-(3,5- dimethylisoxa zol-4-yl)-7-(4- fluoro-2- (trifluorometh yl)phenyl)-1- methyl-1H- benzo[d]imid azol-2(3H)-one</td>
<td><img src="image3" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.18 (s, 1H), 7.81 (dd, $J = 9.5$, 2.4 Hz, 1H), 7.32-7.59 (m, 2H), 7.01 (d, $J = 1.8$ Hz, 1H), 6.79-6.77 (m, 1H), 2.66 (s, 3H), 2.37 (s, 3H), 2.20 (s, 3H); ESI m/z 406 [M + H]+.</td>
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<tr>
<td>Example Compound</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>General procedure</td>
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<tr>
<td>12</td>
<td>5-{3,5-</td>
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<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.04 (s, 1H), 7.76-7.18 (m, 1H), 7.12 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 3.70 (s, 3H), 2.80 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H); ESI m/z 364 [M + H]$^+$.</td>
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<tr>
<td></td>
<td>dimethylisoxa zol-4-yl)-7-(2-methoxy-5-methylphenyl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td></td>
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<tr>
<td>13</td>
<td>5-{3,5-</td>
<td><img src="image2" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.12 (s, 1H), 8.27 (dd, J = 4.9, 1.9 Hz, 1H), 7.78 (dd, J = 7.4, 1.9 Hz, 1H), 7.17-7.10 (m, 1H), 6.98 (d, J = 1.8 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 3.85 (s, 3H), 2.82 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H); ESI m/z 351 [M + H]$^+$.</td>
<td>&gt;99</td>
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<td>dimethylisoxa zol-4-yl)-7-(2-methoxy-5-methylpyridin-3-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
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<tr>
<td>14</td>
<td>3-{6-{3,5-</td>
<td><img src="image3" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.19 (s, 1H), 7.90 (dd, J = 7.7, 1.2 Hz, 1H), 7.68 (dd, J = 8.1, 1.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H); ESI m/z 359 [M + H]$^+$.</td>
<td>&gt;99</td>
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<td>dimethylisoxa zol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-methylbenzonitrile</td>
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<tr>
<td>15</td>
<td>4,6-bis(3,5-dimethylisoxa zol-4-y1)-1,3-dimethyl-1H-benzo[d]imida zol-2(3H)-one</td>
<td><img src="image1" alt="Structure" /></td>
<td>none</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.26 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 1.8 Hz, 1H), 3.40 (s, 3H), 3.00 (s, 3H), 2.43 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 2.09 (s, 3H); ESI m/z 353 [M + H]+.</td>
<td>&gt;99</td>
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<tr>
<td>16</td>
<td>3-(6-(3,5-dimethylisoxa zol-4-y1)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imida zol-4-y1)-4-methylbenzonitrile</td>
<td><img src="image2" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.18 (s, 1H), 7.86-7.81 (m, 2H), 7.59-7.54 (m, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.17 (s, 3H); ESI m/z 359 [M + H]+.</td>
<td>&gt;99</td>
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<td>17</td>
<td>5-(3,5-dimethylisoxa zol-4-y1)-7-(4-methoxyphenyl)-1-methyl-1H-benzo[d]imida zol-2(3H)-one</td>
<td><img src="image3" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.13 (s, 1H), 8.56 (d, J = 5.7 Hz, 1H), 8.40 (s, 1H), 7.20 (d, J = 5.7 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 3.84 (s, 3H), 2.82 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H); ESI m/z 351 [M + H]+.</td>
<td>&gt;99</td>
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<td>18</td>
<td>5-(3,5-dimethylisoxa zol-4-y1)-7-(5-fluoro-2-methoxyphenyl)-1-methyl-1H-benzo[d]imida zol-2(3H)-one</td>
<td><img src="image4" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.09 (s, 1H), 7.33-7.20 (m, 2H), 7.16-7.07 (m, 1H), 6.96 (d, J = 1.7 Hz, 1H), 6.75 (d, J = 1.7 Hz, 1H), 3.72 (s, 3H), 2.82 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H); ESI m/z 366 [M - H]-.</td>
<td>99.0</td>
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<tr>
<td>Example Compound</td>
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<tr>
<td>19</td>
<td>7-(5-chloro-2-methylphenyl)-5-(3,5-dimethylisoxa zol-4-y1)-1-methyl-1H-benzo[d]imida zol-2(3H)-one</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>A</td>
<td>$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 11.11 (s, 1H), 7.42 (dd, $J = 8.0$, 2.5 Hz, 1H), 7.40 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 6.98 (d, $J = 1.5$ Hz, 1H), 6.73 (d, $J = 2.0$ Hz, 1H), 2.71 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H), 2.06 (s, 3H); ESI m/z 368 [M + H]$^+$.</td>
<td>98.6</td>
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<tr>
<td>20</td>
<td>7-(6-amino-2-methylpyridin-3-yl)-5-(3,5-dimethylisoxa zol-4-y1)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>A</td>
<td>$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 11.03 (s, 1H), 7.27 (d, $J = 8.5$ Hz, 1H), 6.92 (d, $J = 1.5$ Hz, 1H), 6.69 (d, $J = 1.5$ Hz, 1H), 6.35 (d, $J = 8.5$ Hz, 1H), 5.97 (s, 2H), 2.82 (s, 3H), 2.39 (s, 3H), 2.22 (s, 3H), 2.07 (s, 3H); ESI m/z 350 [M + H]$^+$.</td>
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<tr>
<td>21</td>
<td>7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxa zol-4-y1)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>A</td>
<td>$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.03 (d, $J = 1.5$ Hz, 1H), 7.35–7.33 (m, 1H), 7.15 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 1.5$ Hz, 1H), 3.02 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H), 2.13 (br.s, 6H); ESI m/z 338 [M + H]$^+$.</td>
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<td>22</td>
<td>6-(3,5-dimethylisoxa zol-4-y1)-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>none</td>
<td>$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 10.7 (s, 1H), 10.4 (s 1H), 6.82 (d, $J = 1.5$ Hz, 1H), 6.68 (d, $J = 1.5$ Hz, 1H), 3.70 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H),</td>
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<td>benzo[d]imida zol-2(3H)-one</td>
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<td>2.12 (s, 3H), 2.05 (s, 3H); ESI m/z 338 [M + H]+.</td>
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<td>-(3,5- dimethylisoxa zol-4-yl)-4- (1,3,5- trimethyl-1H- pyrazol-4-yl)-1H- benzo[d]imida zole-2(3H)- thione</td>
<td><img src="image1" alt="Structure" /></td>
<td>No general procedure</td>
<td>$^1$H NMR (400 MHz, DMSO-d$_6$) δ 12.37 (br.s, 2H), 7.01 (s, 1H), 6.87 (s, 1H), 3.71 (s, 3H), 2.42 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H); ESI MS m/z 352 [M - H]-.</td>
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<td>24</td>
<td>6-(3,5- dimethylisoxa zol-4-yl)-4-(4- methyl[pyridin -3-yl]-1H- benzo[d]imida zole-2-thiol</td>
<td><img src="image2" alt="Structure" /></td>
<td>No general procedure</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) δ 12.58 (br.s, 1H), 11.33 (br.s, 1H), 8.45 (s, 1H), 8.23 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 1.2 Hz, 1H), 6.91 (d, J = 1.2 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H); ESI MS m/z 337 [M + H]+.</td>
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<td>25</td>
<td>3-(6-(3,5- dimethylisoxa zol-4-yl)-2- thiooxo-2,3- dihydro-1H- benzo[d]imida zol-4-yl)-4- methylbenzonitrile</td>
<td><img src="image3" alt="Structure" /></td>
<td>No general procedure</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) δ 10.26 (br.s, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 2.43 (s, 3H), 2.29 (s, 6H); ESI MS m/z 361 [M + H]+.</td>
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<td>26</td>
<td>5-[(3,5-dimethylisoxazol-4-yl)-1-methyl-7-[(1,3,5-trimethyl-1H-pyrazol-4-yl)amino]-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image1" alt="Structure" /></td>
<td>B</td>
<td>$^1$H NMR (500 MHz, CD$_2$OD) $\delta$ 5.45 (s, 1H), 5.89 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H); ESI m/z 367 [M + H]$^+$</td>
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<td>5-[(3,5-dimethylisoxazol-4-yl)-1-methyl-7-[(2-methylpyridin-3-yl)amino]-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image2" alt="Structure" /></td>
<td>B</td>
<td>$^1$H NMR (500 MHz, CD$_2$OD) $\delta$ 7.86 (dd, J = 1.3, 4.8 Hz, 1H), 7.08-7.03 (m, 1H), 6.93 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 6.77 (dd, J = 1.2, 8.2 Hz, 1H), 3.35 (s, 3H), 2.55 (s, 3H), 2.39 (s, 3H), 2.23 (s, 3H); ESI m/z 350 [M + H]$^+$</td>
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<td>28</td>
<td>5-[(5-(hydroxylmethyl)-3-methylisoxazol-4-yl)-1-methyl-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image3" alt="Structure" /></td>
<td>C</td>
<td>$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.08 (s, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.74 (d, J = 1.8 Hz, 1H), 5.65 (t, J = 5.7 Hz, 1H), 4.49 (d, J = 5.7 Hz, 2H), 3.73 (s, 3H), 2.88 (s, 3H), 2.27 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H); ESI m/z 368 [M + H]$^+$</td>
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<tr>
<td>29</td>
<td>3-(6-(3,5-dimethylisoxazol-4-yl)-2-methyl-2-oxo-1H-benzo[d]imidazol-4-yl)-4-methyl benzamide</td>
<td><img src="image1" alt="Structure" /></td>
<td>E</td>
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</table>

$^1$H NMR (500 MHz, DMSO-$_d_6$) $\delta$ 11.11 (br.s, 1H), 7.94 (br.s, 1H), 7.87 (dd, J = 7.8, 2.0 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.31 (br.s, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 1.5 Hz, 1H) 2.67 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H); ESI m/z 377 [M + H]$^+$.

| 30               | 3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-methyl benzamide | ![Structure](image2) | E | 

$^1$H NMR (500 MHz, DMSO-$_d_6$) $\delta$ 11.10 (br.s, 1H), 7.79 (br.s, 1H), 7.45 (br.s, 1H), 7.41 (dd, J = 7.5, 1.5 Hz, 1H), 7.35 (dd, J = 7.5, 1.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 2.69 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H); ESI m/z 377 [M + H]$^+$.

| 31               | 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-((2-methyl)pyridin-3-yl)oxy)-1H-benzo[d]imidazo[2(3H)-one | ![Structure](image3) | No general procedure | 

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.21 (dd, J = 1.5, 4.6 Hz, 1H), 7.31 (dd, J = 1.5, 8.3 Hz, 1H), 7.27 (dd, J = 4.6, 8.4 Hz, 1H), 6.87 (d, J = 1.4 Hz, 1H), 6.49 (d, J = 1.4 Hz, 1H), 3.51 (s, 3H), 2.59 (s, 3H), 2.34 (s, 3H), 2.17 (s, 3H); HPLC 97.0%, tR = 8.5 min; ESI m/z 351 [M + H]$^+$.

*Purity HPLC* indicates the purity level determined by High-Performance Liquid Chromatography (HPLC).
<table>
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<th>Chemical Name</th>
<th>Structure</th>
<th>General procedure</th>
<th>Characterization</th>
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<td>32</td>
<td>7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(5-(hydroxyl methyl)-3-methylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure" /></td>
<td>C</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 12.37 (br.s, 1H), 11.07 (s, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 5.65 (t, J = 5.7 Hz, 1H), 4.49 (d, J = 5.7 Hz, 2H), 2.87 (s, 3H), 2.27 (s, 3H), 2.04 (br.s, 6H); ESI m/z 354 [M + H]+.</td>
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<td>33</td>
<td>5-(3,5-dimethylisoxazol-4-yl)-7-((3,5-dimethyl isoxazol-4-yl)amino)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure" /></td>
<td>B</td>
<td>$^1$H NMR (300 MHz, CD$_2$OD) δ 6.57 (d, J = 1.5 Hz, 1H), 6.02 (d, J = 1.5 Hz, 1H), 3.75 (s, 3H), 2.03 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H); ESI m/z 354 [M + H]+.</td>
<td>95.7</td>
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<td>34</td>
<td>5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(naphthalen-1-yl)-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.2 (s, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.63-7.50 (m, 5H), 7.07 (d, J = 1.5 Hz, 1H), 6.86 (d, J = 1.8 Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H); ESI MS m/z 370 [M + H]+.</td>
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<td>7-(3,5-dichloropyridin-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image" alt="Structure" /></td>
<td>D</td>
<td>$^1$H NMR (500 MHz, CD$_2$OD) δ 8.71 (s, 2H), 7.14 (d, J = 1.6 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 2.97 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H); ESI m/z 389 [M + H]+.</td>
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<td>36</td>
<td>5-((3,5-dimethylisoxa zol-4-yl)-1-methyl-7-(quinolin-3-yl)-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.2 (s, 1H), 9.06 (d, J = 2.4 Hz, 1H), 8.53 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 6.9 Hz, 1H), 7.86-7.80 (m, 1H), 7.72-7.69 (m, 1H), 7.07 (d, J = 1.5 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 2.87 (s, 3H), 2.43 (s, 3H), 2.25 (s, 3H); ESI MS m/z 371 [M + H]$^+$</td>
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<td>37</td>
<td>7-(2-chloro phenyl)-5-(3,5-dimethyl isoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>A</td>
<td>$^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.2 (s, 1H), 7.63-7.43 (m, 4H), 7.01 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 2.76 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H); ESI MS m/z 354 [M + H]$^+$</td>
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<td>38</td>
<td>5-((3,5-dimethylisoxa zol-4-yl)-1-methyl-7-(3-methylpyridin-4-yl)-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>D</td>
<td>$^1$H NMR (500 MHz, CD$_2$OD) δ 8.53 (s, 1H), 8.47 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 5.0 Hz, 1H), 7.09 (d, J = 1.4 Hz, 1H), 6.79 (d, J = 1.4 Hz, 1H), 2.88 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H); ESI m/z 335 [M + H]$^+$</td>
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<td>D</td>
<td>$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.37 (s, 2H), 7.10 (d, $J = 1.6$ Hz, 1H), 6.72 (d, $J = 1.6$ Hz, 1H), 2.82 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), 2.11 (s, 6H); ESI m/z 349 [M + H]$^+$</td>
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<td>$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.1 (s, 1H), 7.35-7.29 (m, 4H), 6.96 (d, $J = 1.8$ Hz, 1H), 6.71 (d, $J = 1.8$ Hz, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.09 (s, 3H); ESI MS m/z 334 [M + H]$^+$</td>
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<td>7-(5-chloro-2-</td>
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<td>$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.1 (s, 1H), 7.51-7.48 (m, 1H), 7.39 (d, $J = 2.7$ Hz, 1H), 7.15 (d, $J = 9.0$ Hz, 1H), 6.96 (d, $J = 1.5$ Hz, 1H), 6.75 (d, $J = 1.5$ Hz, 1H), 3.74 (s, 3H), 2.82 (s, 3H), 2.40 (s, 3H), 2.22 (s,</td>
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<td>5-(3,5-&lt;br&gt;dimethylisoxa&lt;br&gt;zol-4-yl)-7-(2-fluoro-3-&lt;br&gt;methoxyphenyl)-1-methyl-1H-benzo[d]&lt;br&gt;imidazol-2(3H)-one</td>
<td>![Structure Image]</td>
<td>A</td>
<td>³H NMR (300 MHz, DMSO-d6) δ 11.2 (s, 1H), 7.28-7.21 (m, 2H), 7.06-7.01 (m, 2H), 6.81 (d, J = 1.5 Hz, 1H), 3.89 (s, 3H), 2.85 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H); ESI MS m/z 384 [M + H]⁺.</td>
<td>&gt;99</td>
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<td>5-(3,5-&lt;br&gt;dimethylisoxa&lt;br&gt;zol-4-yl)-7-(2,4-dimethyl&lt;br&gt;thiazol-5-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td>![Structure Image]</td>
<td>A</td>
<td>³H NMR (300 MHz, DMSO-d6) δ 11.2 (s, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.83 (d, J = 1.5 Hz, 1H), 2.94 (s, 3H), 2.66 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H); ESI MS m/z 355 [M + H]⁺.</td>
<td>&gt;99</td>
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<td>45</td>
<td>5-(3,5-&lt;br&gt;dimethylisoxa&lt;br&gt;zol-4-yl)-7-(2-methoxy-6-&lt;br&gt;methylpyridin-3-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td>![Structure Image]</td>
<td>A</td>
<td>³H NMR (300 MHz, DMSO-d6) δ 11.1 (s, 1H), 7.65 (d, J = 7.2 Hz, 1H), 6.99 (s, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 3.82 (s, 3H), 2.83 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H); ESI MS m/z 365 [M + H]⁺.</td>
<td>&gt;99</td>
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### Example 1: Inhibition of Tetra-acetylated Histone H4 Binding Individual BET Bromodomains

[0192] Proteins were cloned and overexpressed with a W-terminal 6×His tag, then purified by nickel affinity followed by size exclusion chromatography. Briefly, E.coli BL21(DE3) cells were transformed with a recombinant expression vector encoding /N-terminally Nickel affinity tagged bromodomains from Brd2, Brd3, Brd4. Cell cultures were incubated at 37°C with shaking to the appropriate density and induced overnight with IPTG. The supernatant of lysed cells was loaded onto Ni²⁺-IDA column for purification. Eluted protein was pooled, concentrated and further purified by size exclusion chromatography. Fractions representing monomeric protein were pooled, concentrated, aliquoted, and frozen at -80°C for use in subsequent experiments.

[0193] Binding of tetra-acetylated histone H4 and BET bromodomains was confirmed by a Homogenous Time Resolved Fluorescence Resonance Energy Transfer (HTRF®) method. 

<table>
<thead>
<tr>
<th>Example Compound</th>
<th>Chemical Name</th>
<th>Structure</th>
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<th>Characterization</th>
<th>Purity HPLC</th>
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<td>7-(benzo[d] oxazol-5-yl)-5-(3,5-dimethyl isoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>A</td>
<td>νH NMR (300 MHz, DMSO-d6) δ 11.2 (s, 1H), 8.85 (s, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.56-7.53 (m, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 2.79 (s, 3H), 2.42 (s, 3H), 2.24 (s, 3H); ESI MS m/z 361 [M + H]^+.</td>
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<td>7-(cyclohex-1-en-1-yl)-5-(3,5-dimethyl isoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>A</td>
<td>νH NMR (300 MHz, DMSO-d6) δ 11.0 (s, 1H), 6.82 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H), 5.68-5.67 (m, 1H), 3.30 (s, 3H), 2.38 (s, 3H), 2.29-2.27 (m, 2H), 2.20 (s, 3H), 2.19-2.18 (m, 2H), 1.77-1.65 (m, 4H); ESI MS m/z 324 [M + H]^+.</td>
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terminally His-tagged bromodomains (200 nM) and biotinylated tetra-acetylated histone H4 peptide (25-50 nM, Millipore) were incubated in the presence of Europium Cryptate-labeled streptavidin (Cisbio Cat. #610SAKLB) and XL665-labeled monoclonal anti-His antibody (Cisbio Cat. #61H1SXLB) in a white 96 well microliter plate (Greiner). For inhibition assays, serially diluted test compound was added to these reactions in a 0.2% final concentration of DMSO. Duplicate wells were used for each concentration tested. Final buffer concentrations were 30 mM HEPES pH 7.4, 30 mM NaCl, 0.3 mM CHAPS, 20 mM phosphate pH 7.0, 320 mM KF, 0.08% BSA. After a 2 h incubation at room temperature, fluorescence was measured at 665 and 620 nm with a SynergyH4 plate reader (Biotek). The binding inhibitory activity was shown by a decrease in 665 nm relative to 620 nm fluorescence. IC₅₀ values were determined from a dose response curve.

[0194] Compounds with an IC₅₀ value less than or equal to 0.3 µM were deemed to be highly active (+++); compounds with an IC₅₀ value between 0.3 and 3 µM were deemed to be very active (++); compounds with an IC₅₀ value between 3 and 30 µM were deemed to be active (+).

Table 2: Inhibition of Tetra-acetylated Histone H4 Binding to Brd4 bromodomain 1 (BRD4(1)) as Measured by FRET

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<tr>
<th>Example Compound</th>
<th>FRET activity BRD4(1)</th>
<th>Example Compound</th>
<th>FRET activity BRD4(1)</th>
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<th>FRET activity BRD4(1)</th>
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</table>
Example 2: Inhibition of c-MYC expression in cancer cell lines

[0195] V4-11 cells (CRL-9591) were plated at a density of 2.5x10⁴ cells per well in 96 well U-bottom plates and treated with increasing concentrations of test compound or DMSO (0.1%) in IMDM media containing 10% FBS and penicillin/streptomycin, and incubated for 3 h at 37°C. Triplicate wells were used for each concentration. Cells were pelleted by centrifugation and harvested using the mRNA Catcher PLUS kit according to manufacturer’s instructions. The eluted mRNA isolated was then used in a one-step quantitative real-time PCR reaction, using components of the RNA UltraSense™ One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for cMYC and Cyclophilin. Real-time PCR plates were run on a ViiA™7 real time PCR machine (Applied Biosystems), data was analyzed, normalizing the Ct values for hMYC to an internal control, prior to determining the fold expression of each sample, relative to the control.

[0196] Compounds with an IC₅₀ value less than or equal to 0.3 µM were deemed to be highly active (+++); compounds with an IC₅₀ value between 0.3 and 3 µM were deemed to be very active (++); compounds with an IC₅₀ value between 3 and 30 µM were deemed to be active (+).
Table 3: inhibition of c-myc Activity in Human AMI MV4-11 cells

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Example 3: inhibition of cell proliferation in cancer cell lines

[0197] In this example, cell titer in MV4-11 cells were quantitated to measure the inhibition of proliferation when treated with a compound of the present disclosure.

[0198] MV4-11 cells (CRL-9591) were plated at a density of 5x10⁴ cells per well in 96 well flat bottom plates and treated with increasing concentrations of test compound or DMSO (0.1%) in 1%DM media containing 1.0% FBS and penicillin/streptomycin. Triplicate wells were used for each concentration and a well containing only media was used as a control. Plates were incubated at 37°C, 5% CO₂ for 72 h before adding 20 μL of the CellTiter Aqueous One Solution (Promega) to each well and incubated at 37°C, 5% CO₂ for an additional 3-4 h. The absorbance was read at 490 nm in a
spectrophotometer and the percentage of cell titer relative to DMSO-treated cells was calculated after correcting for background by subtracting the blank well’s signal. IC$_{50}$ values were calculated using the GraphPad Prism software.

[0199] Compounds with an IC$_{50}$ value less than or equal to 0.3 µM were deemed to be highly active (+++); compounds with an IC$_{50}$ value between 0.3 and 3 µM were deemed to be very active (++); compounds with an IC$_{50}$ value between 3 and 30 µM were deemed to be active (+).

Table 4: inhibition of Cell Proliferation in Humari AMI iVIV-4-li cells

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</table>
Example 4: inhibition of hIL-6 mRNA Transcription

[0200] In this example, hIL-6 mRNA in tissue culture cells were quantitated to measure the transcriptional inhibition of hIL-6 when treated with a compound of the present disclosure.

[0201] Human leukemic monocyte lymphoma U937 cells (CRL-1593.2) were plated at a density of 3.2x10^4 cells per well in a 96-well plate in 100 µL RPMI-1640 containing 10% FBS and penicillin/streptomycin, and differentiated into macrophages for 3 days in 60 ng/mL PMA (pseudobol-13-myristate-12-acetate) at 37°C in 5% CO2 prior to the addition of compound. The cells were pretreated for 1 h with increasing concentrations of test compound in 0.1% DMSO prior to stimulation with 1 µg/mL lipopolysaccharide from Escherichia coli. Triplicate wells were used for each concentration. The cells were incubated at 37°C, 5% CO2 for 3 h before the cells were harvested. At time of harvest, media was removed and cells were rinsed in 200 µL PBS. Cells were harvested using the mRNA Catcher PLUS kit according to manufacturer’s instructions. The eluted mRNA was then used in a one-step quantitative real-time PGR reaction using components of the RNA UltraSense™ One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for hIL-6 and Cyclophilin. Real-time PGR plates were run on a ViiA™7 real time PGR machine (Applied Biosystems), data was analyzed, normalizing the Ct values for hIL-6 to an internal control, prior to determining the fold expression of each sample, relative to the control.

[0202] Compounds with an IC_{50} value less than or equal to 0.3 µM were deemed to be highly active (+++); compounds with an IC_{50} value between 0.3 and 3 µM were deemed to be very active (++); compounds with an IC_{50} value between 3 and 30 µM were deemed to be active (+).
### Example 5: inhibition of hIL-17 mRNA Transcription

[0203] In this example, hIL-17 mRNA in human peripheral blood mononuclear cells were quantitated to measure the transcriptional inhibition of hIL-17 when treated with a compound of the present disclosure.

[0204] Human peripheral blood mononuclear cells were plated (2.0x10^6 cells per well) in a 96-well plate in 45 µl Optimizer T Cell expansion media (Life Technologies) containing 20 ng/ml IL-2 and penicillin/streptomycin. The cells were treated with increasing concentrations of the test compound or DMSO (0.1%), and incubated at 37°C, 5% CO2 for 1 h before addition of 10X stock OKT3 antibody at 10 ug/ml in media. Triplicate wells were used for each concentration. Cells were incubated at 37°C, 5% CO2 for 6 h before the cells were harvested. At time of harvest, cells were pelleted by centrifugation at 800 rpm for 5 min. Cells were harvested using the mRNA Catcher PLUS kit according to manufacturer's instructions. The eluted mRNA was then used in a one-step quantitative real-time PCR reaction, using components of the RNA UltraSense™ One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for hIL-17 and Cyclophilin. Real-time PCR plates were run on a ViiA™7 real time PCR machine (Applied Biosystems), data was

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Table S: Inhibition of hIL-6 mRNA Transcription
analyzed, normalizing the Ct values for hL-17 to an internal control, prior to determining the fold induction of each unknown sample, relative to the control.

[0206] Compounds with an IC₅₀ value less than or equal to 0.3 µM were deemed to be highly active (+++); compounds with an IC₅₀ value between 0.3 and 3 µM were deemed to be very active (++); compounds with an IC₅₀ value between 3 and 30 µM were deemed to be active (+).

Table 6: inhibition of hL-17 mRNA Transcription

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Example 6: inhibition of hVCAm mRNA Transcription

[0206] In this example, hVCAm mRNA in tissue culture cells is quantitated to measure the transcriptional inhibition of hVCAm when treated with a compound of the present disclosure.

[0207] Human umbilical vein endothelial cells (HUVECs) are plated in a 96-well plate (4×10⁵ cells per well) in 100 µL EGM media and incubated for 24 h prior to the addition of increasing concentrations of the compound of interest or DMSO (0.1%). Triplicate wells were used for each concentration. The cells are pretreated for 1 h with the test compound prior to stimulation with tumor necrosis factor-α when they are incubated for an additional 24 h before the cells are harvested. At time of harvest, the spent media is removed and HUVECs are rinsed in 200 µL PBS. Cells were harvested using the mRNA Catcher PLUS kit according to manufacturer’s instructions. The eluted mRNA was then used in a one-step quantitative real-time PCR reaction, using components of the RNA UltraSense™ One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for hVCAm and Cyclophilin. Real-time PCR plates were run on a ViiA™7 real time PCR
machine (Applied Biosystems), data was analyzed, normalizing the Ct values for hVCA to an internal control, prior to determining the fold induction of each unknown sample, relative to the control.

Example 7: inhibition of hMCP-1 mRNA Transcription

[0208] In this example, hMCP-1 mRNA in human peripheral blood mononuclear cells is quantitated to measure the transcriptional inhibition of hMCP-1 when treated with a compound of the present disclosure.

[0209] Human Peripheral Blood Mononuclear Cells are plated at a density of $1.0 \times 10^5$ cells per well in a 96-well plate in RPMI-1640 containing 10% FBS and penicillin/streptomycin. The cells are treated with increasing concentrations of the compound or DMSO (0.1%), and incubated at 37°C, 5% CO2 for 3 h before the cells are harvested. At time of harvest, cells are transferred to V-bottom plates and pelleted by centrifugation at 800 rpm for 5 min. Cells were harvested using the mRNA Catcher PLUS kit according to manufacturer’s instructions. The eluted mRNA was then used in a one-step quantitative real-time PCR reaction, using components of the TaqMan® One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for hMCP-1 and Cyclophiiin. Real-time PCR plates were run on a ViiA™7 real time PCR machine (Applied Biosystems), data was analyzed, normalizing the Ct values for hMCP-1 to an internal control, prior to determining the fold induction of each unknown sample, relative to the control.

Example 8: Up-regulation of hApoA-l mRNA Transcription,

[0210] In this example, hApoA-l mRNA in tissue culture cells was quantitated to measure the transcriptional up-regulation of hApoA-l when treated with a compound of the present disclosure.

[0211] Huh-7 cells (2.5x10^5 per well) were plated in a 96-well plate using 100 µL DM EM per well, (Gibco DMFM supplemented with penicillin/streptomycin and 10% FBS), 72 h before the addition of the compound. The cells are treated with increasing concentrations of the compound or DMSO (0.1%), and incubated at 37°C, 5% CO2 for 48 h. Spent media was removed from the Huh-7 cells and placed on ice for immediate use with the "LDH cytotoxicity assay Kit II" from Abeam. The cells remaining in the plate were rinsed with 100 µl PBS, Cells were harvested using the mRNA Catcher PLUS kit according to manufacturer’s instructions. The eluted mRNA was then used in a one-step quantitative real-time PCR reaction, using components of the TaqMan® One-Step Kit (Life Technologies) together with Applied Biosystems TaqMan® primer-probes for hApoA-l and Cyclophiiin, Real-time PCR plates were run on a ViiA™7 real time PCR machine (Applied Biosystems),
data was analyzed, normalizing the Ct values for hApoA-1 to an internal control, prior to determining
the fold induction of each unknown sample, relative to the control.

[0212] Compounds with an EC<sub>70</sub> value less than or equal to 0.3 µM were deemed to be
highly active (+++); compounds with an EC<sub>70</sub> value between 0.3 and 3 µM were deemed to be very
active (++); compounds with an EC<sub>70</sub> value between 3 and 30 µM were deemed to be active (+).

Table 7: Up-regulation of hApoA-1 mRNA Transcription.

<table>
<thead>
<tr>
<th>Example</th>
<th>ApoA-1 activity</th>
<th>Example</th>
<th>ApoA-1 activity</th>
<th>Example</th>
<th>ApoA-1 activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+++</td>
<td>4</td>
<td>+++</td>
<td>7</td>
<td>+++</td>
</tr>
<tr>
<td>9</td>
<td>+++</td>
<td>13</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 9: <i>in vivo</i> efficacy in athymic nude mouse strain of an acute myeloid leukemia xenograft
model using SV1V4-11 cells:

[0213] MV4-11 cells (ATCC) were grown under standard cell culture conditions and (NCr)
nu/nu fiso] strain of female mice age 6-7 weeks were injected with 5x 10<sup>6</sup> cells/animal in 100 µl PBS
+ 100 µl Matrigel in the lower left abdominal flank. By approximately day 18-21 after MV4-11 cells
injection, mice were randomized based on tumor volume (L x W x H)/2) of average ~100-300 mm<sup>3</sup>. Mice were dosed orally with compound at 5 to 120 mg/kg b.i.d and/or q.d. on a continuous dosing
schedule and at 2.5 to 85 mg/kg q.d. on a 5 day on 2 day off, 100mg/kg q.d. on a 4 day on and 3 day
off, 13S mg/kg q.d. on a 3 day on and 4 day off, 180mg/kg on a 2 day on and 5 day off and 240
mg/kg on a 1 day on and 6 days off dosing schedules in EA006 formulation at 10 ml/kg body weight
dose volume. Tumor measurements were taken with electronic micro calipers and body weights
measured on alternate days beginning from dosing period. The average tumor volumes, percent
Tumor Growth Inhibition (TGI) and % change in body weights were compared relative to Vehicle
control animals. The means, statistical analysis and the comparison between groups were calculated
using Student's t-test in Excel.
Table 8: *in vivo* efficacy in athymic nude mouse strain of an acute myeloid leukemia xenograft model

<table>
<thead>
<tr>
<th>Example Compound</th>
<th><em>in vivo activity</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 9</td>
<td>Active</td>
</tr>
</tbody>
</table>

Example 10: *in vivo* efficacy in athymic nude mouse strain of an acute myeloid leukemia xenograft model using OCI-3 AML cells

[0214] OCI-3 AML cells (DMS2) were grown under standard cell culture conditions and (NCr) rstit/nufiso! strain of female mice age 6-7 weeks were injected with 10 x 10^6 cells/animal in 100 µL PBS + 100 µL Matrigel in the lower left abdominal flank. By approximately day 18-21 after OCI-3 AML cells injection, mice were randomized based on tumor volume (L x W x H)/2 of average ~100-300 mm^3. Mice were dosed orally with compound at 30mg/kg b.i.d on a continuous dosing schedule and at 2.5 to 45 mg/kg q.d. on a 5 day on and 2 day off dosing schedule in EA006 formulation at 10 mL/kg body weight dose volume. Tumor measurements were taken with electronic micro calipers and body weights measured on alternate days beginning from dosing period. The average tumor volumes, percent Tumor Growth inhibition (TGI) and % change in body weights were compared relative to Vehicle control animals. The means, statistical analysis and the comparison between groups were calculated using Student’s t-test in Excel.

Table 9: *in vivo* efficacy in athymic nude mouse strain of an acute myeloid leukemia xenograft model using OCI-3 AML cells

<table>
<thead>
<tr>
<th>Example Compound</th>
<th><em>in vivo activity</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 9</td>
<td>Active</td>
</tr>
</tbody>
</table>

Example 11: Evaluation of Target Engagement.

[0215] MV4-11 and MM.1.s cells (ATCC) were grown under standard cell culture conditions and (NCr) nu/nu fiso! strain of female mice age 6-7 weeks were injected with 5 x 10^6 cells/animal in 100 µL PBS + 100 µL Matrigel in the lower left abdominal flank. By approximately day 28 after MV4-11 and MM.1.s cells injection, mice were randomized based on tumor volume (L x W x H)/2 of average ~500 mm^3. Mice were dosed orally with compound in EA006 formulation at 10
mL/kg body weight dose volume and tumors harvested 3, 6, 12, 24 hrs post dose for Bci2 and c-myc gene expression analysis as PD biomarkers.

Table 10: Evaluation of Target Engagement.

<table>
<thead>
<tr>
<th>Example Compound</th>
<th>In vivo activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 9</td>
<td>Active</td>
</tr>
</tbody>
</table>

Example 12: *In vivo* efficacy in athymic nude mouse strain of multiple myeloma xenograft model using MM1.s cells

MM1.s cells (ATCC) were grown under standard cell culture conditions and SCID-Beige strain of female mice age 6-7 weeks were injected with 10x10⁶ cells/animal in 100 μL PBS + 100 μL Matrigel in the lower left abdominal flank. By approximately day 21 after MM1.s cells injection, mice were randomized based on tumor volume (L x W x H)/2) of average ~120 mm³. Mice were dosed orally with compound at 25 to 90 mg/kg b.i.d and or q.d in EAOQS formulation at 10 mL/kg body weight dose volume. Tumor measurements were taken with electronic micro calipers and body weights measured on alternate days beginning from dosing period. The average tumor volumes, percent Tumor Growth inhibition (TGI) and % change in body weights were compared relative to Vehicle control animals. The means, statistical analysis and the comparison between groups were calculated using Student's t-test in Excel.

Table 11: *In vivo* efficacy in athymic nude mouse strain of multiple myeloma xenograft model using MM1.s cells

<table>
<thead>
<tr>
<th>Example Compound</th>
<th>In vivo activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 9</td>
<td>Active</td>
</tr>
</tbody>
</table>

Example 13: *In Vivo* Efficacy in Mouse Endotoxemia Model Assay.

Sub lethal doses of Endotoxin (E. Coli bacterial lipopolysaccharide) are administered to animals to produce a generalized inflammatory response which is monitored by increases in secreted cytokines. Compounds are administered to C57/Bl6 mice at T= 4 hours orally at 75 mg/kg dose to evaluate inhibition in IL-6 and IL-17 and MCP-1 cytokines post 3-h challenge with lipopolysaccharide (LPS) at T=0 hours at 0.5 mg/kg dose intraperitoneal.
Example 14: \textit{in Vivo} Efficacy in Rat Collagen-Induced Arthritis

[0218] Rat collagen-induced arthritis is an experimental model of polyarthritis that has been widely used for preclinical testing of numerous anti-arthritic agents. Following administration of collagen, this model establishes a measurable polyarticular inflammation, marked cartilage destruction in association with pannus formation and miid to moderate bone resorption and periosteal bone proliferation. In this model, collagen was administered to female Lewis strain of rats on Day 1 and 7 of study and dosed with compounds from Day 11 to Day 17. Test compounds were evaluated to assess the potential to inhibit the inflammation (including paw swelling), cartilage destruction and bone resorption in arthritic rats, using a model in which the treatment is administered after the disease has been established.

Example 15: \textit{In Vivo} Efficacy in Experimental autoimmune encephalomyelitis (EAE) Model of MS

[0219] Experimental autoimmune encephalomyelitis (EAE) is a T-cell-mediated autoimmune disease of the CMS which shares many clinical and histopathological features with human multiple sclerosis (MS). EAE is the most commonly used animal model of MS. T cells of both Th1 and Thl7 lineage have been shown to induce EAE. Cytokines IL-23, IL-6 and IL-17, which are either critical for Th1 and Thl7 differentiation or produced by these T cells, play a critical and non-redundant role in EAE development. Therefore, drugs targeting production of these cytokines are likely to have therapeutic potential in treatment of MS.

[0220] Compounds of Formula I were administered to EAE mice to assess anti-inflammatory activity. In this model, EAE is induced by \textit{M}0 \text{G} \text{p} \text{p} \text{C} \text{CFA} immunization and pertussis toxin injection in female C57Bl/6 mice.

Example 16: \textit{Ex Vivo} effects on T cell function from Splenocyte and Lymphocyte cultures stimulated with external M0G stimulation

[0221] Mice were immunized with M06/CFA and simultaneously treated with the compound for 11 days on a b.i.d regimen. Inguinal Lymph node and spleen were harvested, cultures were set up for lymphocytes and splenocytes and stimulated with external antigen (MOG) for 72 hours. Supernatants from these cultures were analyzed for TH1, Th2 and Thl7 cytokines using a Cytometric Bead Array assay.

[0222] Other embodiments of the present disclosure will be apparent to those skilled in the art from consideration of the specification and practice of the present disclosure disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the present disclosure being indicated by the following claims.
What is claimed is:

1. A compound of Formula I:

   \[
   \begin{array}{c}
   R_3 \quad X \\
   \downarrow \\
   W_1 \\
   \downarrow \\
   W_3 \\
   \downarrow \\
   W_4 - W_2 \\
   \end{array}
   \]

   or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof,

   wherein:

   A is a 5-membered monocyclic heterocycle having the formula

   \[
   \begin{array}{c}
   Y \quad Z_1 \quad W_3 \\
   \downarrow \\
   A \\
   \downarrow \\
   Z_2 \quad W_4 \\
   \end{array}
   \]

   and is fused to ring B to form an A-B bicyclic ring,

   B is a six-membered carbocycle or heterocycle;

   W_1 is selected from N and CR_1;

   W_2 is CR_2;

   W_3 and W_4 are C;

   R_1 and R_2 are independently selected from hydrogen, deuterium, alkyl, -OH, -NH_, -thioalkyl, and alkoxy;

   X is optionally present, and if present, is selected from --(NH)--, -NHCR_3R_4-, -NHSO_2-, oxygen, -CH_2CH_2-, -CH=CH-, -CR_3R_4N-, -OOCR_3R_4-, -CR_3R_4O-, -SCR_3R_4-, -CR_3R_4S-, where S might be oxidized to sulfoxide or sulfone, or -NHC(O)-, wherein the nitrogen is connected to the B ring;

   Y is selected from 0 and S;

   Z_1 and Z_2 are independently selected from oxygen and -N-R_2;

   each R_4 is independently selected from hydrogen, deuterium, and alkyl (C_3-)}
R and R are each independently selected from hydrogen, alkyl(C₃₋₅), halogen, -OH, -CF₃, deuterium, amino, alkoxy(C₁₋₅), or two substituents selected from Rₐ; Rₐ and Rₜ may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;

Rₐ is selected from hydrogen, 4-7-membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;

with the proviso that Rₐ cannot be hydrogen if X is different from -NH₂, and

D₁ is selected from 5-membered monocyclic carbocycles and heterocycles connected to the B-ring via a carbon-carbon bond,

with the proviso that D₁ cannot be a substituted or unsubstituted furan, thiophene, cyclopentane, tetrahydrofuran, and tetrahydrothiophene.

2. The compound of claim 1, wherein the A-B ring is a substituted or unsubstituted

![Chemical Structure]

3. A compound of Formula IA:

![Chemical Structure]

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof,

wherein:

W₁ is selected from N and CR₁;

R₁ and R₂ are independently selected from hydrogen, deuterium, alkyl, -OH, -NH₂, -thioalkyl, and alkoxy;

¥ is selected from O and S;

Z₁ and Z₂ are independently selected from oxygen and -N·Rₜ;

each Rₜ is independently selected from hydrogen, deuterium, and alkyl (C₁₋₅);

X is optionally present, and if present, is selected from -(NH) -, -NHCR₁R₂, -NHSO₂-, oxygen, -CH₂CH₂-, -CH=CH-, -CR₁R₂NH-, -OCR₁R₂, -CR₁R₂O-, -SCR₁R₂, -CR₁R₂S-, where S might be oxidized to sulfoxide or sulfone, or -NHC(O)-, wherein the nitrogen is connected to the 8 ring;
R<sub>i</sub> and R<sub>j</sub> are each independently selected from hydrogen, alkyl(C<sub>i</sub>-), halogen, -OH, -CF<sub>3</sub>, deuterium, amino, alkoxy(C<sub>i</sub>-), or two substituents selected from R<sub>i</sub>, R<sub>j</sub> and R<sub>i</sub> may be connected in a 5- or 6-membered ring to form a bicyclic carbocycle or bicyclic heterocycle;

R<sub>i</sub> is selected from hydrogen, 4-7-membered carbocycles, 4-7-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles;

with the proviso that R<sub>i</sub> cannot be hydrogen if X is different from -NH-, and

D is selected from 5-membered monocyclic carbocycles and heterocycles connected to the B-ring via a carbon-carbon bond,

with the proviso that D cannot be a substituted or unsubstituted furan, thiophene, cyclopentane, tetrahydrofuran, and tetrahydrothiophene.

4. The compound according to any one of claims 1 to 3, wherein the A-B bicyclic ring is selected from

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5. The compound according to any one of claims 1 to 4, wherein the A-B bicyclic ring is selected from

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6. The compound according to claim 5, wherein the A-B bicyclic ring is selected from

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7. The compound according to any one of claims 1 to 6, wherein the A-B bicyclic ring is selected from

\[
\begin{array}{c}
R_8 \\
X \rightarrow R_3 \\
R_1 \\
R_2 \Downarrow D_1
\end{array}
\]

8. The compound of any one of claims 1 to 8, wherein \( R_2 \) is selected from hydrogen and methyl.

9. The compound of any one of claims 1 to 8, wherein one or more hydrogen atoms is replaced with deuterium.

10. The compound of any one of claims 1 to 9, wherein \( D_1 \) is selected from a 5-membered monocyclic heterocycle selected from

\[
\begin{array}{c}
N \\
O \\
S \\
\end{array}
\]

wherein the \( D_1 \) ring is optionally substituted with one or more deuterium, alkyl(C\(_1\)-C\(_8\)) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C\(_1\)-C\(_4\)) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH\(^+\), -NHMe, -NHEt, -NHPr, -NHBu, -NMe\(_2\), -NMeEt, -NEt\(_2\), -NEtBu, -NHCO(N)Halkyl), halogen (such as F, Cl), amide (such as -NHCO(N)Me, -NHCO(N)Et, -C(O)Me, -C(O)Et, -C(O)Pr), -S(O)\(_2\)alkyl(C\(_1\)-C\(_4\)) (such as -S(O)\(_2\)Me, -S(O)\(_2\)Et, -S(O)\(_2\)Pr, -S(O)\(_2\)Bu), -COOH, and/or ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu), wherein said alkyl(C\(_1\)-C\(_4\)), alkoxy(C\(_1\)-C\(_4\)), amino, amide, ketone (Ci-C\(_4\)), -S(G)alkyl(C\(_1\)-C\(_4\)), -SO\(_2\)alkyl(C\(_1\)-C\(_4\)), -thioalkyl(C\(_1\)-C\(_4\)), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH\(^+\), -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

11. The compound of any one of claims 1 to 10, wherein \( D_1 \) is selected from a 5-membered monocyclic heterocycle selected from
optionally substituted with one or more deuterium, alky(C1-C4) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C1-C4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH2, -NHMe, -NHiPr, -NHiBu, -NHMe2, NMeEt, -NEt2, -NEtBu, -NHCO(0)Nalkyl), halogen (such as F, Cl), amide (such as -NHCO(0)Me, -NHCO(0)Et, -C(0)NHMe, -C(0)NEt2, -C(0)NiPr), -CF3, CN, -N2, ketone (C1-C4) (such as acetyl, -C(O)Et, -C(O)Pr), -SOalkyl(C1-C4) (such as -S02Me, -SO2Et, -SO2Pr), -thioalkyl(C1-C4) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and/or ester (such as -COOMe, -C(O)Et, -C(O)OBu), wherein said alky(C1-Q), alkoxy(C1-C4), amino, amide, ketone (C1-C4), -SOalkyl(C1-C4), -thioalkyl(CyGx), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

12. The compound of any one of claims 1 to 11, wherein D1 is optionally substituted with one or more deuterium, alky(C1-C4) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C1-C4) (such as methoxy, ethoxy, isopropoxy), wherein said alky(C1-C4) and alkoxy(C1-C4) may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, or -NH2.

13. The compound of any one of claims 1 to 9 or 12, wherein D2 is selected from a 5-membered monocyclic heterocycle containing one oxygen and one or two nitrogens, where the hetero(CyGx) is connected to the rest of the molecule via a carbon-carbon bond, optionally substituted with one or more deuterium, alky(C1-C4) (such as methyl, ethyl, propyl, isopropyl, butyl) optionally substituted with one or more F, Cl, Br, -OH, or -NH2.

14. The compound of any one of claims 1 to 13, wherein D4 is a 1 isoxazole or pyrazole optionally substituted with one or more deuterium, alky(C1-C4) (such as methyl, ethyl, propyl, isopropyl, butyl) which may be optionally substituted with one or more F, -OH, or -NH2.

15. The compound of any one of claims 1 to 14, wherein D4 is an isoxazole optionally substituted with one or two groups independently selected from deuterium, alky(C1-C4) (such as methyl, ethyl, propyl, isopropyl, butyl) optionally substituted with one or more hydrogen, F, -OH, or -NH2.

16. The compound of any one of claims 1 to 15, wherein D4 is

17. The compound of any one of claims 1 to 16, wherein Z1 is -NRa, and Ra is methyl.

18. The compound of any one of claims 1 to 17, wherein Z2 is oxygen.

19. The compound of any one of claims 1 to 18, wherein W1 is CRa.

20. The compound of any one of claims 1 to 19, wherein X is optionally present, and if present, is selected from - (NH) - , -NHRaRb, -NH50 - , oxygen, -CH2CH2 - , -CH=CH2, -CRaRbNH2.
OCR R y - , -CR R 0-..-SCR R y , where S might be oxidized to sulfoxide or sulfone, or -NHC(O)-, wherein
the nitrogen is connected to the B ring.

21. The compound of any one of claims 1 to 20, wherein X is optionally present, and if present, is selected from -(N H)-, -NHCR R y R y , -CR R y NH-.

22. The compound of any one of claims 1 to 21, wherein X is not present.

23. The compound of any one of claims 1 to 20, wherein X is oxygen.

24. The compound of any one of claims 1 to 21, wherein X is -NH- and R y is hydrogen.

25. The compound of any one of claims 1 to 21, wherein R x and R y are each independently selected from hydrogen, alkyl(C n-3), halogen, -OH, -CF 3, deuterium, amino, and alkoxy(C n-3).

26. The compound of any one of claims 1 to 21, wherein R x and R y are each independently selected from hydrogen, methyl, halogen, -CF 3, and deuterium.

27. The compound of any one of claims 1 to 26, wherein R x is selected from hydrogen, deuterium, alkyl, -OH, and -NH 2.

28. The compound of any one of claims 1 to 27, wherein R x is selected from hydrogen and methoxy.

29. The compound of any one of claims 1 to 27, wherein R x is selected from hydrogen, deuterium, -NH 2, and methyl.

30. The compound of any one of claims 1 to 29, wherein R x is hydrogen.

31. The compound of any one of claims 1 to 30, wherein R x is selected from hydrogen, -Br, and -NH 2.

32. The compound of any one of claims 1 to 31, wherein R x is hydrogen.

33. The compound of any one of claims 1 to 32, wherein R x is selected from 5-6 membered carbocycles, 5-6-membered heterocycles, bicyclic carbocycles, and bicyclic heterocycles.

34. The compound of any one of claims 1 to 33, wherein R x is selected from 5-6 membered heterocycles.

35. The compound of any one of claims 1 to 34, wherein R x is selected from 5-6 membered heterocycles containing 1 or 2 nitrogens, such as unsubstituted and substituted pyrimidyl rings.

36. The compound of any one of claims 1 to 35, wherein R x is selected from 6-membered heterocycles containing at least one nitrogen, such as unsubstituted and substituted pyridyl rings.

37. The compound of any one of claims 1 to 32, wherein R x is selected from
optionally substituted with one or more groups independently selected from deuterium, alkyl(C\_1-C\_4) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C\_1-C\_4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH\_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe\_2, NMe\_Et, -NEt\_2, -NEtBu, -NHC(O)NHalkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(0)N H\_2, -C(0)NHMe, -C(0)NHET, -C(0)NiPr), -S(O)Et, -S(O)Pr, -SMe, -COOH), and/or ester (such as -C(O)OBu), wherein said alkyl(C\_1-C\_4), alkoxy(C\_1-C\_4), amino, amide, ketone (C\_1-C\_4), thioalkyl(C\_1-C\_4), -S(O)alkyl(C\_1-C\_4), thioalkyl(C\_1-C\_4), and ester may be optionally substituted with one or more F, Cl, Br, -OH, -NH\_2, -NHMe, -OMe, -SM, oxo, and/or thio-oxo.

38. The compound of claim 37, wherein \( \frac{1}{4} \) is selected from

optionally substituted with one or more one or more groups independently selected from deuterium, alkyl(Cl-C\_2) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C\_1-C\_4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH\_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe\_2, NMe\_Et, -NEt\_2, -NEtBu, -NHC(O)NHalkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(0)N H\_2, -C(0)NHMe, -C(0)NHET, -C(0)NiPr), -S(O)Et, -S(O)Pr, -SMe, -COOH), and CN.

39. The compound of any one of claims 1 to 35, wherein \( R_3 \) is an isoxazooie or pyrazoie optionally substituted with one or more groups independently selected from deuterium, alkyl(C\_1-C\_4) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C\_1-C\_4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH\_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe\_2, NMe\_Et, -NEt\_2, -NEtBu, -NHC(O)NHalkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(0)N HMe, -
C(O)NB₂, -C(O)NiPr, -CF₃, CN, -N₃, ketone (C₁-C₄) (such as acetyl, -C(O)Et, -C(O)Pr, -S(O)Alkyl(C₁-C₄) (such as S(O)Me, S(Et), -SO₂Alkyl(C₁-C₄) (such as -SO₂Et, -SO₂Pr), thioalkyl (C₁-C₄) (such as -SMe, -Et, -Pr, -Bu), carboxyl (such as -COOH), and/or ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBU₃, wherein said alkyl(C₁-C₄), alkoxy(C₁-C₄), amino, amide, ketone (C₁-C₄), -S(O)Alkyl(C₁-C₄), -SO₂alkyl(C₁-C₄), thioalkyl (C₁-C₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, OH, NH₂, -NMe₂, -OMe, -SMe, oxo, and/or thio-oxo.

40. The compound of any one of claims 1 to 33, wherein R₃ is selected from 5-6 membered carbocycles, such as a substituted or unsubstituted phenyl ring.

41. The compound of any one of claims 1 to 40, wherein R₃ is substituted with a group selected from Methyl, -CF₃, -OCF₃, -OME, -OEt, MeOCH₃, -Cl, -F, -CM, -NH₂, -C(O)NH₂, -C(O)NHMe, -NHC(O)CH₃, N,N-dimethylamirnoretmyl, -SG₂Me, and oxo.

42. The compound of any one of claims 1 to 41, wherein R₃ is optionally substituted with one or more methyl, CF₃, -OCF₃, methoxy, ethoxy, methoxymethyl, Cl, CN, F, -NH₂, amide (-CNH₂, -CONHMe, -NHC(O)CH₃), -COOH, -COOMe, IM, N-dimethylaminomethyl, -S0₂Me, and oxo.

43. The compound of any one of claims 1 to 32, wherein R₃ is selected from

![Chemical structures](image-url)
-SMe, -SEt, -SPr, -SBu), carboxyi (such as -COOH), and/or ester (such as -C(0)OMe, -C(0)OEt, -C(Q)OBu), wherein said alkyl(C1-C4), alkoxy(C1-C4), amino, amide, ketone (C1-C4), -S(Q)Alkyl(C1-C4), -SO2alkyl(C1-C4), -thioalkyl(C1-C4), and ester may be optionally substituted with one or more F, Cl, Br, -OH, -NH2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

44. The compound of claim 43, wherein R3 is selected from

![Chemical structure](image)

45. The compound of any one of claims 1 to 20, wherein \(-X-R_3\) is selected from -NHaryl-

46. The compound of claim 45, wherein R3 is pyridyl.

47. The compound of any one of claims 1 to 3, wherein the A-B bicyclic ring is selected from

![Chemical structure](image)

\(D_A\) is an isoxazole or pyrazole optionally substituted with one or more deuterium, alkyl(C1-C4)(such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C1-C4)(such as methoxy, ethoxy, isopropoxy), amino (such as -NH, -NHMe, -NHPr, -NHBU, -NMe2, NMeEt, -NET2, -NETBu, -NH(C)(NH)alkyl), halogen (such as F, Cl), amide (such as -NH(C)(0)Me, -NH(C)(0)Et, -C(0)NHMe, -C(0)NEt, -C(0)NPr, -C(0)NEt2, -C(0)NPr2), CN, -N3, ketone (C1-C4) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C1-C4) (such as -S(0)Me, -S(0)Et, -S(0)Pr), -thioalkyl(C1-C4) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and/or ester (such as -C(0)OMe, -C(0)OEt, -C(Q)OBu), wherein said alkyl(C1-C4), alkoxy(C1-C4), amino, amide, ketone (C1-C4), -S(0)Alkyl(C1-C4), -SO2alkyl(C1-C4), -thioalkyl(C1-C4), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo;

X is optionally present, and if present, is selected from -NH-, -O-, -NHCR, -NH=, -NHS02-, -CR=NR-, and

\(Z_1\) is - NR3; and

\(R_3\) is an isoxazole, pyrazole, pyridyl, thiazole, isothiazole, pyrimidine, phenyl, cyclohexene, benzo[d]oxazolyl, naphthyl, or quinoiyl, optionally substituted with one or more groups independently selected from deuterium, alkyl(C1-C4)(such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C1-C4) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH, -NHMe, -NHET, -NHPr, -NHBU, -
NMe₂, NH₂Et, -NEt₂, -NEtBu, -NHC(Q)Nalkyl), halogen (such as F, Cl), amide (such as -NHC(0)Me, -NHC(0)Et, -C(0)NEt₂, -C(0)NiPr), -CF₃, CN, -N₃, ketone (C₁-C₄) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C₁-C₄) (such as -S(0)Me, -S(0)Et, -S(0)₂Et, -S(0)₂Pr), -thioalkyl(C₁-C₄), amino, amide, ketone (Cr₄), -S(0)Alkyl(C₁-C₄), -SO₂alkyl(C₁-C₄), -thioalkyl(C₁-C₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo,
or if X is -(NH)- then R₃ may also be hydrogen.

48. The compound of claim 3, wherein the A-B bicyclic ring is selected from

D₁ is an isoxazole or pyrazole optionally substituted with one or more deuterium, alkyl(C₁-C₄) (such as methyl, ethyl, propyl, isopropyl, butyl), a(koxy(C₁-C₄) (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NHMe, -NHEt, -NHiPr, -NHBu -NMe₂, NMeEt, -NEt₂, -NEtBu, -NHC(O)NMethylalkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NEt₂, -C(O)NiPr), -C(O)cycloamino, -CF₃, CN, -N₃, ketone (C₁-C₄) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C₁-C₄) (such as -S(0)Me, -S(0)Et, -S(0)₂Et, -S(0)₂Pr), -thioalkyl(C₁-C₄), -SO₂alkyl(C₁-C₄), -thioalkyl(C₁-C₄), amino, amide, ketone (Cr₄), -S(0)Alkyl(C₁-C₄), -thioalkyl(C₁-C₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo;

X is optionally present, and if present, is selected from - (NH)₂, -NHCR₄R₇⁻, -NHSO₂⁻,
-CR₄R₇NH⁻;

R₃ is an isoxazole, pyrazole, pyridyl, thiazole, isothiazole, pyrimidine, phenyl, cyclohexene, benzo idoxazolyl, nathylo, or quinonyl, optionally substituted with one or more groups independently selected from deuterium, alkyl(C₁-C₄) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, aikxy(C₁-C₄) (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NHMe, -NHiPr, -NHBu -NMe₂, NMeEt, -NEt₂, -NEtBu, -NHC(O)NMethylalkyl), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NEt₂, -C(O)NiPr), -C(O)cycloamino, -CF₃, CN, -N₃, ketone (C₁-C₄) (such as acetyl, -C(0)Et, -C(0)Pr), -S(0)Alkyl(C₁-C₄) (such as -S(0)Me, -S(0)Et, -S(0)₂Et, -S(0)₂Pr), -thioalkyl(C₁-C₄), -SO₂alkyl(C₁-C₄), -thioalkyl(C₁-C₄), amino, amide, ketone (Cr₄), -S(0)Alkyl(C₁-C₄), -thioalkyl(C₁-C₄), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo;
(C₃₋₄ₐ₃), -S(0)alkyl(C₃₋₄ₐ₃), -SO₂alkyl(C₃₋₄ₐ₃), thioalkyl(C₃₋₄ₐ₃), and ester may be optionally substituted with one or more hydrogen, F, Cl, Br, -OH, -NH₂, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo, or if X is ~{NHR} then R₃ may also be hydrogen.

49. The compound of 48, wherein the A-B bicyclic ring is from

or if X is ~{NHR} then R₃ may also be hydrogen.

49. The compound of 48, wherein the A-B bicyclic ring is from

R₃ is an isoxazole, pyrazole, or pyridyl optionally substituted with one or more groups independently selected from deuterium, alkyl(C₃₋₄ₐ₃) (such as methyl, ethyl, propyl, isopropyl, butyl), -OH, alkoxy(C₃₋₄ₐ₃) (such as methoxy, ethoxy, isoproxy), amino (such as -NH₂, -NHMe, -NHC₃, -NHPr, -NHBu, -NMₑₑ₂, -NMe₃, -NH₂Me), halogen (such as F, Cl), -CF₃.

50. A compound of Formula 1 or Formula 1 A selected from:

4.6-bis(3,5-dimethylisoxazol-4-yl)-lH-benzo[d]imidazo[l-2(3H)-one;
5.7-bis(3,5-dimethylisoxazol-4-yl)-l-methyl-lH-benzo[d]imidazo[2(3H)-one;
5,7-bis(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(2-methylpyridin-3-yl)-lH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(2-(trifluoromethyl)phenyl)-lH-benzo[d]imidazo[2(3H)-one;
7-(1,3-dimethyl-lH-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-l-methyl-lH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(2-(trifluoromethyl)pyridin-3-yl)-lH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(1,3,5-trimethyl-lH-pyrazol-4-yl)-lH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(4-methylisothiazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-methoxy-5-methylphenyl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-methoxypyridin-3-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-methylibenzonitrile;
4,6-bis(3,5-dimethylisoxazol-4-yl)-13-dimethyl-1H-benzo[d]imidazol-2(3H)-one;
3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-4-methylibenzonitrile;
5-(3,5-dimethylisoxazol-4-yl)-7-(4-methoxypyridin-3-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(5-fluoro-2-methoxyphenyl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
7-(5-chloro-2-methylphenyl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
7-(6-amino-2-methylpyridin-3-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one;
6-(3,5-dimethylisoxazol-4-yl)-4-(13,5-trimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one;
6-(3,5-dimethylisoxazol-4-yl)-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-2(3H)-thione;
6-(3,5-dimethylisoxazol-4-yl)-4-(4-methylpyridin-3-yl)-1H-benzo[d]imidazol-2-thiol;
3-(6-(3,5-dimethylisoxazol-4-yl)-2-thioxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-4-methylbenzonitrile;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(13,5-trimethyl-1H-pyrazol-4-yl)amino)-1H-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(2-methylpyridin-3-yl)amino)-1H-benzo[d]imidazol-2(3H)-one;
3-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-lH-benzo[d]imidazo[4-yl)-4-methylbenzamide;
3-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-lH-benzo[d]imidazo[4-yl)-2-methylbenzamide;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-((2-methyIpyridin-3-yl)oxy)-lH-benzo[d]imidazol-2(3H)-one;
7-(3,5-dimethyl-lH-pyrazol-4-yl)-5-(5-(hydroxymethyl)-3-methylisoxazol-4-yl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(naphthalen-1-yl)-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(naphthalen-1-yl)-lH-benzo[d]imidazo[2(3H)-one;
7-(3,5-dichloropyridin-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-lH-benzo[d]imidazo[2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(quinolin-3-yl)lH-benzoidimidazo l-2 (3H)-one;
7-(2-chloropheny!)5-(3,5-dimethylisoxazol-4-yl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(3-methylpyridin-4-yl)-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(3,5-dimethylpyridin-4-yl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-l-methyl-7-(o-tolyl)-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-fluoro-5-methoxyphenyl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
7-(5-chloro-2-methoxyphenyl)-5-(3,5-dimethylisoxazol-4-yl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-(2-fluoro-3-methoxyphenyl)-l-riethyl-lH-benzoEdimidazol-2(3H)-one;
S-iS^-dimethylisoxazol^-yi^-iZ^dimethyIthiazol-S-YO-l-methyi-IH-benzoldlimfdazol-
2(3H)-one;
5-(3,5-dimethylisoxazol-4-yl)-7-((2-methoxy-6-methylpyridin-3-yl)-l-methyl-lH-benzo[d]imidazol-2(3H)-one;
7-[(benzimidazo)oxazol-5-yl]-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one; and

7-(cyclohex-l-ene-l-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one,

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

51. A pharmaceutical composition comprising the compound of any one of claims 1-50 or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, and a pharmaceutically acceptable carrier.

52. A method for inhibition of BET protein function comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

53. A method of treating an autoimmune or inflammatory disorder associated with BET proteins comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

54. The method of claim 53, wherein the autoimmune or inflammatory disorder is selected from Acute Disseminated Encephalomyelitis, Agammaglobulinemia, Allergic Disease, Ankylosing spondylitis, Anti-G BM/Anti-TBM nephritis, Anti-phospholipid syndrome, Autoimmune aplastic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune myocarditis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura, Behcet’s Disease, Bifious pemphigoid, Castieman’s Disease, Celiac Disease, Churg-Strauss syndrome, Crohn's Disease, Cogan's syndrome, Dry eye syndrome, Essential mixed cryoglobulinemia, Dermatomyositis, Devic’s Disease, Encephalitis, Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Giant cell arteritis, Glomerulonephritis, Goodpasture’s syndrome, Granulomatosis with Polyangiitis (Wegener’s), Graves’ Disease, Guillain-Barre syndrome, Hashimoto’s thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, IgA nephropathy, Inclusion body myositis, Type 1 diabetes, Interstitial cystitis, Kawasaki’s Disease, Leukocytoclastic vasculitis, Lichen planus, Lupus (SLE), Microscopic polyangiitis, Multiple sclerosis, Myasthenia gravis, myositis, Optic neuritis, Pemphigus, POEMS syndrome, Polyarteritis nodosa, Primary biliary cirrhosis, Psoriasis, Psoriatic arthritis, Pyoderma gangrenosum, Relapsing polychondritis, Rheumatoid arthritis, Sarcoidosis, Scleroderma, Sjogren’s syndrome, Takayasu’s arteritis, Transverse myelitis, Ulcerative colitis, Uveitis, and Vitiligo.

55. A method of treating an acute or chronic non-autoimmune inflammatory disorder characterized by disregulation of IL-6 and/or IL-17 comprising administering a therapeutically
effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

56. The method of claim 55, wherein the acute or chronic non-autoimmune inflammatory disorder is selected from sinusitis, pneumonitis, osteomyelitis, gastritis, enteritis, gingivitis, appendicitis, irritable bowel syndrome, tissue graft rejection, chronic obstructive pulmonary disease (COPD), septic shock, osteoarthritis, acute gout, acute lung injury, acute renal failure, burns, Herxheimer reaction, and SIRS associated with viral infections.

57. The method of claim 55, wherein the acute or chronic non-autoimmune inflammatory disorder is selected from rheumatoid arthritis (RA) and multiple sclerosis (MS).

58. A method of treating a cancer associated with overexpression, translocation, amplification, or rearrangement of a myc family oncprotein that is sensitive to BET inhibition comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

59. The method of claim 58, wherein the cancer is selected from [B-acute lymphocytic leukemia, Burkitt's lymphoma, Diffuse large cell lymphoma, Multiple myeloma, Primary plasma cell leukemia, Atypical carcinoid lung cancer, Bladder cancer, Breast cancer, Cervix cancer, Colon cancer, Gastric cancer, Glioblastoma, Hepatocellular carcinoma, Large cell neuroendocrine carcinoma, Medulloblastoma, Melanoma, nodular, Melanoma, superficial spreading, Neuroblastoma, esophageal squamous cell carcinoma, Osteosarcoma, Ovarian cancer, Prostate cancer, Renal clear cell carcinoma, Retinoblastoma, Rhabdomyosarcoma, and Small cell lung carcinoma.

60. A method of treating a cancer associated with overexpression, translocation, amplification, or rearrangement of BET proteins comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

61. The method of claim 60, wherein the cancer is selected from NUT midline carcinoma, B-cell lymphoma, non-small cell lung cancer, esophageal cancer, head and neck squamous cell carcinoma, and colon cancer.

62. A method of treating a cancer that relies on pTEFb (Cdk9/cyclin T) and BET proteins to regulate oncogenes comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

63. The method of claim 62, wherein the cancer is selected from chronic lymphocytic leukemia and multiple myeloma, follicular lymphoma, diffuse large B cell lymphoma with germinal center phenotype, Burkitt's lymphoma, Hodgkin's lymphoma, follicular lymphomas and activated,
anaplastic large cell lymphoma, neuroblastoma and primary neuroectodermal tumor, rhabdomyosarcoma, prostate cancer, and breast cancer,

64. A method of treating a cancer associated with upregulation of BET responsive genes CDK6, Bcl2, TYR03, MYB, and bTERT comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51,

65. The method of claim 64, wherein the cancer is selected from pancreatic cancer, breast cancer, colon cancer, glioblastoma, adenoid cystic carcinoma, T-cell prolymphocyte leukemia, malignant glioma, bladder cancer, medulloblastoma, thyroid cancer, melanoma, multiple myeloma, Barret's adenocarcinoma, hepatoma, prostate cancer, pro-myelocytic leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, diffuse large B-cell lymphoma, small cell lung cancer, and renal carcinoma.

66. A method of treating a cancer that is sensitive to effects of BET inhibition comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

67. The method of claim 66, wherein the cancer is selected from NUT-midline carcinoma (NMV), acute myeloid leukemia (AML), acute B lymphoblastic leukemia (B-ALL), Burkitt's Lymphoma, B-cell Lymphoma, Melanoma, mixed lineage leukemia, multiple myeloma, pro-myelocytic leukemia (PML), non-Hodgkin's lymphoma, Neuroblastoma, Medulloblastoma, lung carcinoma (NSCLC, SCLC), and colon carcinoma.

68. The method of any one of claims 58-67, wherein the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 is combined with other therapies, chemotherapeutic agents or antiproliferative agents.

69. The method of claim 68, wherein the therapeutic agent is selected from ABT-737, Azacitidine (Vidaza), AZD1152 (Barasertib), AZD2281 (Olaparib), AZD6244 (5e1umetinib), BF.Z235, Bleomycin Sulfate, Bortezomib (Velcade), Busulfan (Myleran), Camptothecin, Cisplatin, Cyclophosphamide (Clafen), CYT387, Cytarabine (Ara-C), Decarbazine, DAPT (GSI-IX), Decitabine, Dexamethasone, Doxorubicin (Adriamycin), Etoposide, Everolimus (RAD001), Flavopiridol (A vocidib), Ganetespib (STA-9090), Gefitinib (Iressa), Idoxuridine, Ifofamide (Mitoxana), IFNa2a (Roferon A), Melphaian (Alkeran), Methazolastone (temozolomide), Metformin, Mitoxantrone (Novantrone), Paclitaxel, Phenformin, PKC412 (Midostaurin), PLX4032 (Vemurafenib), Pomalidomide (CC-4047), Prednisone (Deltasone), Rapamycin, Revlimid (Lenalidomide), Ruxolitinib (INCBO18424), Sorafenib (Nexavar), SU11248 (Sunitinib), SU11274, Vinblastine, Vincristine (Oncovin), Vinorelbine (Navelbine), Vorinostat (SANA), PD-1 and PD-L1 inhibitors (pembrolizumab, nivolumab, yervoy ipiiimumab), and VVP1130 (Degrasyn).
70. A method of treating a benign proliferative or fibrotic disorder, selected from the group consisting of benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, menigioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, juvenile polyposis syndrome, idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, and cardiac fibrosis comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

71. A method of treating a disease or disorder that benefits from up-regulation or ApoA-1 transcription and protein expression comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

72. The method of claim 71, wherein the disease is cardiovascular disease, dyslipidemia, atherosclerosis, hypercholesterolemia, metabolic syndrome, and Alzheimer’s disease.

73. A method of treating a metabolic disease or disorder comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

74. The method of claim 73, wherein the metabolic disorder is selected from obesity-associated inflammation, type II diabetes, and insulin resistance.

75. A method of treating a cancer associated with a virus comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

76. The method of claim 75, wherein the virus is selected from Epstein-Barr Virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi’s sarcoma associated virus (KSHV), human papilloma virus (HPV), Merkel cell polyomavirus, and human cytomegalovirus (CMV).

77. A method for treating HIV infection comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 alone or in combination with anti-retroviral therapeutic.

78. A method for treating a disease or disorder selected from Alzheimer’s disease, Parkinson’s disease, Huntington disease, bipolar disorder, schizophrenia, Rubinstein-Taybi syndrome, and epilepsy comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.
79. A method of male contraception comprising administering a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51.

80. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for the manufacture of a medicament for use in a method of for treating according to any one of claims 52-79.

81. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a disease or condition associated with BET by inhibiting a BET protein function.

82. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 in method of treating an autoimmune or inflammatory disorder associated with BET proteins.

83. The use according to claim 82, wherein the autoimmune or inflammatory disorder is selected from Acute Disseminated Encephalomyelitis, Agammaglobulinemia, Allergic Disease, Ankylosing spondylitis, Anti-G BM/Anti-TBM nephritis, Anti-phospholipid syndrome, Autoimmune aplastic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune myocarditis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura, Behcet's Disease, Bullous pemphigoid, Castleman's Disease, Celiac Disease, Churg-Strauss syndrome, Crohn's Disease, Cogan's syndrome, Dry eye syndrome, Essential mixed cryoglobulinemia, Dermatomyositis, Devic's Disease, Encephalitis, Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Giant cell arteritis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (Wegener's), Graves' Disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schoniein purpura, idiopathic pulmonary fibrosis, IgA nephropathy, inclusion body myositis, Type I diabetes, Interstitial cystitis, Kawasaki's Disease, Leukocytoclastic vasculitis, Lichen planus, Lupus (SLE), Microscopic polyangiitis, Multiple sclerosis, Myasthenia gravis, myositis, Optic neuritis, Pemphigus, POEMS syndrome, Polyarteritis nodosa, Primary biliary cirrhosis, Psoriasis, Psoriatic arthritis, Pyoderma gangrenosum, Relapsing polychondritis, Rheumatoid arthritis, Sarcoidosis, Scleroderma, Sjogren's syndrome, Takayasu's arteritis, Transverse myelitis, Ulcerative colitis, Uveitis, and Vitiligo.

84. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating an acute or chronic non-autoimmune inflammatory disorder characterized by disregulation of IL-6 and/or IL-17.

85. The use according to claim 54, wherein the acute or chronic non-autoimmune inflammatory disorder is selected from sinusitis, pneumonia, osteomyelitis, gastritis, enteritis,
gingivitis, appendicitis, irritable bowel syndrome, tissue graft rejection, chronic obstructive pulmonary disease (COPD), septic shock, osteoarthritis, acute gout, acute lung injury, acute renal failure, burns, Herxheimer reaction, and SIRS associated with viral infections.

86. The use according to claim 84, wherein the acute or chronic non-autoimmune inflammatory disorder is selected from rheumatoid arthritis (RA) and multiple sclerosis (MS).

87. The use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer associated with overexpression, translocation, amplification, or rearrangement of a myc family oncoprotein that is sensitive to BET inhibition.

88. The use according to claim 87, wherein the cancer is selected from B-acute lymphocytic leukemia, Burkitt's lymphoma, Diffuse large cell lymphoma, Multiple myeloma, Primary plasma cell leukemia, Atypical carcinoid lung cancer, Bladder cancer, Breast cancer, Cervix cancer, Colon cancer, Gastric cancer, Glioblastoma, Hepatocellular carcinoma, Large cell neuroendocrine carcinoma, Ivledulloblastoma, Melanoma, nodular, Melanoma, superficial spreading, Neuroblastoma, esophageal squamous cell carcinoma, Osteosarcoma, Ovarian cancer, Prostate cancer, Renal clear cell carcinoma, Retinoblastoma, Rhabdomyosarcoma, and Small cell lung carcinoma.

89. The use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer associated with overexpression, translocation, amplification, or rearrangement of BET proteins.

90. The use according to claim 89, wherein the cancer is selected from NUT midline carcinoma, B-cell lymphoma, non-small cell lung cancer, esophageal cancer, head and neck squamous cell carcinoma, and colon cancer.

91. The use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer that relies on pTEFb (Cdk9/cyclin T) and BET proteins to regulate oncogenes.

92. The use according to claim 91, wherein the cancer is selected from chronic lymphocytic leukemia and multiple myeloma, follicular lymphoma, diffuse large B-cell lymphoma with germinal center phenotype, Burkitt's lymphoma, Hodgkin's lymphoma, follicular lymphomas and activated, anaplastic large cell lymphoma, neuroblastoma and primary neuroectodermal tumor, rhabdomyosarcoma, prostate cancer, and breast cancer.

93. The use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer associated with upregulation of BET responsive genes CDK6, Bcl2, TYR03, MYB, and hTERT.
94. The use according to claim 93, wherein the cancer is selected from pancreatic cancer, breast cancer, colon cancer, glioblastoma, adenoid cystic carcinoma, T-cell prolymphocytic leukemia, malignant glioma, bladder cancer, medulloblastoma, thyroid cancer, melanoma, multiple myeloma, Barret's adenocarcinoma, hepatoma, prostate cancer, pro-myelocytic leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, diffuse large B-cell lymphoma, small cell lung cancer, and renal carcinoma.

95. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer that is sensitive to effects of BET inhibition.

96. The use according to claim 95, wherein the cancer is selected from NUT-midline carcinoma (N-M), acute myeloid leukemia (AML), acute B lymphoblastic leukemia (B-ALL), Burkitt's Lymphoma, B-cell Lymphoma, Melanoma, mixed lineage leukemia, multiple myeloma, pro-myelocytic leukemia (PML), non-Hodgkin's lymphoma, Neuroblastoma, Medulloblastoma, lung carcinoma (NSCLC, SCLC), and colon carcinoma.

97. The use according to any one of claims 81-96, wherein the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 is combined with other therapies, chemotherapeutic agents or antiproliferative agents.

98. The use according to claim 97, wherein the therapeutic agent is selected from ABT-737, Azacitidine (Vidaza), AZD1152 (Barasertib), AZD2281 (Olaparib), AZD5244 (Seiumetinib), BEZ235, Bleomycin Sulfate, Bortezomib (Velcade), Busulfan (Myleran), Camptothecin, Cisplatin, Cyclophosphamide (Clafen), CYT387, Cytarabine (ara-C), Dacarbazine, DAPT (GSI-IX), Decitabine, Dexamethasone, Doxorubicin (Adradymin), Etoposide, Everolimus (RAD001), Flavopiridol (Alvocidib), Ganetespib (STA-9090), Gefitinib (Iressa), Idarubicin, Ifosfamide (Mitoxana), IFNα2a (Roferon A), Meiphalan (Alkeran), Methoxyamine (temozolomide), Metformin, Mitoxantrone (Novartis), Paclitaxel, Phenformin, PKC412 (Midostaurin), PLX4032 (Vemurafenib), Pomaaidomide (CC-4047), Prednisone (Deltaone), Rapamycin, Revimid (Lenalidomide), Ruxolitinib (INCBO18424), Sorafenib (Nexavar), SU11248 (Sunitinib), SU11274, Vinblastine, Vincristine (Oncovin), Vinoreibine (Navebine), Vorinostat (SAN), and VVP1130 (Degrasyn).

99. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a benign proliferative or fibrotic disorder, selected from the group consisting of benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, menigioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord
nODULES, POLYPS, AND CYSTS, CASTLEMAN DISEASE, CHRONIC PILONIDAL DISEASE, DERMATOFIBROMA, PILAR CYST, PYOGENIC GRANULOMA, JUVENILE POLYPOSIS SYNDROME, IDIOPATHIC PULMONARY FIBROSIS, RENAL FIBROSIS, POST-OPERATIVE STRICTURE, KELOID FOMATION, SCLERODERMA, AND CARDIAC FIBROSIS.

100. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a disease or disorder that benefits from up-regulation or ApoAI transcription and protein expression.

101. The use according to claim 100, wherein the disease is cardiovascular disease, dyslipidemia, atherosclerosis, hypercholesterolemia, metabolic syndrome, and Alzheimer's disease.

102. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a metabolic disease or disorder.

103. The use according to claim 102, wherein the metabolic disorder is selected from obesity-associated inflammation, type II diabetes, and insulin resistance.

104. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a cancer associated with a virus.

105. The use according to claims 104, wherein the virus is selected from Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma associated virus (KSHV), human papilloma virus (HPV), Merkel cell polyomavirus, and human cytomegalovirus (CMV).

106. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51, alone or in combination with an anti-retroviral therapeutic for treating HIV infection.

107. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for treating a disease or disorder selected from Alzheimer's disease, Parkinson's disease, Huntington disease, bipolar disorder, schizophrenia, Rubinstein-Taybi syndrome, and epilepsy.

108. Use of a therapeutically effective amount of the compound of any one of claims 1-50 or a pharmaceutical composition according to claim 51 for male contraception.