[19] Patents Registry
The Hong Kong Special Administrative Region
香港特別行政區
專利註冊處

[11] 1245248 B
EP 3230277 B1

[12] **STANDARD PATENT (R) SPECIFICATION**
轉錄標準專利說明書

[21] Application no. 申請編號
18104394.4

[22] Date of filing 提交日期
03.04.2018

[51] Int. Cl.
C07D 403/14 (2006.01) A61K 31/4196 (2006.01)
A61K 31/4439 (2006.01) A61K 31/4985 (2006.01)
C07D 401/14 (2006.01) C07D 403/04 (2006.01)
C07D 413/14 (2006.01) A61P 35/00 (2006.01)
A61P 37/00 (2006.01)

[54] SUBSTITUTED HETEROCYCLES AS BROMODOMAIN INHIBITORS
被取代的雜環作為溴結構域抑制劑

[30] Priority 優先權
11.12.2014 US 62/090,853

[43] Date of publication of application 申請發表日期
24.08.2018

[45] Date of publication of grant of patent 批予專利的發表日期
15.05.2020

[86] International application no. 國際申請編號
PCT/IB2015/002479

[87] International publication no. and date 國際申請發表編號及日期
WO2016/092375 16.06.2016

EP Application no. & date 歐洲專利申請編號及日期
EP 15866917.6 11.12.2015

EP Publication no. & date 歐洲專利申請發表編號及日期
EP 3230277 18.10.2017

Date of grant in designated patent office 指定專利當局批予專利日期
18.09.2019

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 230 277 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
18.09.2019 Bulletin 2019/38

(21) Application number: **15866917.6**

(22) Date of filing: **11.12.2015**

(51) Int Cl.:
C07D 403/14 *(2006.01)* ***A61K 31/4196*** *(2006.01)*
A61K 31/4439 *(2006.01)* ***A61K 31/4985*** *(2006.01)*
C07D 401/14 *(2006.01)* ***C07D 403/04*** *(2006.01)*
C07D 413/14 *(2006.01)* ***A61P 35/00*** *(2006.01)*
A61P 37/00 *(2006.01)*

(86) International application number:
PCT/IB2015/002479

(87) International publication number:
WO 2016/092375 (16.06.2016 Gazette 2016/24)

(54) SUBSTITUTED HETEROCYCLES AS BROMODOMAIN INHIBITORS

SUBSTITUIERTE HETEROCYCLEN ALS BROMDOMÄNENINHIBITOREN

HÉTÉROCYCLES SUBSTITUÉS À TITRE D'INHIBITEURS DE BROMODOMAINES

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **11.12.2014 US 201462090853 P**

(43) Date of publication of application:
18.10.2017 Bulletin 2017/42

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CA-A1- 2 895 905

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- **CHUNG CHUN-WA ET AL.: 'Discovery and characterization of small molecule inhibitors of the BET family bromodomains' J. MED. CHEM. vol. 54, no. 11, 2011, pages 3827 - 3838, XP002722914**

EP 3 230 277 B1

Description

[0001] The invention provides novel compounds, pharmaceutical compositions containing such compounds, and their use in prevention and treatment of diseases and conditions associated with bromodomain and extra terminal domain (BET) proteins.

[0002] Post-translational modifications (PTMs) of histones are involved in regulation of gene expression and chromatin organization in eukaryotic cells. Histone acetylation at specific lysine residues is a PTM that is regulated by histone acetylases (HATs) and deacetylases (HDACs). Peserico, A. and C. Simone, "Physical and functional HAT/HDAC interplay regulates protein acetylation balance," J Biomed Biotechnol, 2011:371832 (2011). Small molecule inhibitors of HDACs and HATs are being investigated as cancer therapy. Hoshino, I. and H. Matsubara, "Recent advances in histone deacetylase targeted cancer therapy" Surg Today 40(9):809-15 (2010); Vernarecci, S., F. Tosi, and P. Filetici, "Tuning acetylated chromatin with HAT inhibitors: a novel tool for therapy" Epigenetics 5(2):105-11 (2010); Bandyopadhyay, K., et al., "Spermidinyl-CoA-based HAT inhibitors block DNA repair and provide cancer-specific chemo- and radiosensitization," Cell Cycle 8(17):2779-88 (2009); Arif, M., et al., "Protein lysine acetylation in cellular function and its role in cancer manifestation," Biochim Biophys Acta 1799(10-12):702-16 (2010). Histone acetylation controls gene expression by recruiting protein complexes that bind directly to acetylated lysine via bromodomains. Sanchez, R. and M.M. Zhou, "The role of human bromodomains in chromatin biology and gene transcription," Curr Opin Drug Discov Devel 12(5):659-65 (2009). One such family, the bromodomain and extra terminal domain (BET) proteins, comprises Brd2, Brd3, Brd4, and BrdT, each of which contains two bromodomains in tandem that can independently bind to acetylated lysines, as reviewed in Wu, S.Y. and C.M. Chiang, "The double bromodomain-containing chromatin adaptor Brd4 and transcriptional regulation," J Biol Chem 282(18):13141-5 (2007).

[0003] 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. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," Nat Rev Cancer 12(7):465-77 (2012); Prinjha, R.K., J. Witherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains," Trends Pharmacol Sci 33(3):146-53 (2012).

[0004] Autoimmune diseases, which are often chronic and debilitating, are a result of a dysregulated immune response, which leads the body to attack its own cells, tissues, and organs. Pro-inflammatory cytokines including IL-1β, TNF-α, IL-6, MCP-1, and IL-17 are overexpressed in autoimmune disease. IL-17 expression defines the T cell subset known as Th17 cells, which are differentiated, in part, by IL-6, and drive many of the pathogenic consequences of autoimmune disease. Thus, the IL-6/Th17 axis represents an important, potentially druggable target in autoimmune disease therapy. Kimura, A. and T. Kishimoto, "IL-6: regulator of Treg/Th17 balance," Eur J Immunol 40(7):1830-5 (2010). BET inhibitors are expected to have anti-inflammatory and immunomodulatory properties. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," Nat Rev Cancer 12(7):465-77 (2012); Prinjha, R.K., J. Witherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains," Trends Pharmacol Sci 33(3):146-53 (2012). BET inhibitors have been shown to have a broad spectrum of anti-inflammatory effects *in vitro* including the ability to decrease expression of pro-inflammatory cytokines such as IL-1β, MCP-1, TNF-α, and IL-6 in activated immune cells. Mirguet, O., et al., "From ApoA1 upregulation to BET family bromodomain inhibition: discovery of I-BET151," Bioorg Med Chem Lett 22(8):2963-7 (2012); Nicodeme, E., et al., "Suppression of inflammation by a synthetic histone mimic," Nature 468(7327):1119-23 (2010); Seal, J., et al., "Identification of a novel series of BET family bromodomain inhibitors: binding mode and profile of I-BET151 (GSK1210151A)," Bioorg Med Chem Lett 22(8):2968-72 (2012). The mechanism for these anti-inflammatory effects may involve BET inhibitor disruption of Brd4 co-activation of NF-κB-regulated pro-inflammatory cytokines and/or displacement of BET proteins from cytokine promoters, including IL-6. Nicodeme, E., et al., "Suppression of inflammation by a synthetic histone mimic," Nature 468(7327):1119-23 (2010); Zhang, G., et al., "Down-regulation of NF-kappaB Transcriptional Activity in HIVassociated Kidney Disease by BRD4 Inhibition," J Biol Chem, 287(34):8840-51 (2012); Zhou, M., et al., "Bromodomain protein Brd4 regulates human immunodeficiency virus transcription through phosphorylation of CDK9 at threonine 29," J Virol 83(2):1036-44 (2009). In addition, because Brd4 is involved in T-cell lineage differentiation, BET inhibitors may be useful in inflammatory disorders characterized by specific programs of T cell differentiation. Zhang, W.S., et al., "Bromodomain-Containing-Protein 4 (BRD4) Regulates RNA Polymerase II Serine 2 Phosphorylation in Human CD4+ T Cells," J Biol Chem (2012).

[0005] The anti-inflammatory and immunomodulatory effects of BET inhibition have also been confirmed *in vivo.* A BET inhibitor prevented endotoxin- or bacterial sepsis-induced death and cecal ligation puncture-induced death in mice, suggesting utility for BET inhibitors in sepsis and acute inflammatory disorders. Nicodeme, E., et al., "Suppression of inflammation by a synthetic histone mimic," Nature 468(7327):1119-23 (2010). A BET inhibitor has been shown to

ameliorate inflammation and kidney injury in HIV-1 transgenic mice, an animal model for HIV-associated nephropathy, in part through inhibition of Brd4 interaction with NF-κB. Zhang, G., et al., "Down-regulation of NF-kappaB Transcriptional Activity in HIV associated Kidney Disease by BRD4 Inhibition," J Biol Chem 287(34):8840-51 (2012). The utility of BET inhibition in autoimmune disease was demonstrated in a mouse model of multiple sclerosis, where BET inhibition resulted in abrogation of clinical signs of disease, in part, through inhibition of IL-6 and IL-17. 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). These results were supported in a similar mouse model where it was shown that treatment with a BET inhibitor inhibited T cell differentiation into pro-autoimmune Th1 and Th17 subsets *in vitro,* and further abrogated disease induction by pro-inflammatory Th1 cells. Bandukwala, H.S., et al., "Selective inhibition of CD4+ T-cell cytokine production and autoimmunity by BET protein and c-Myc inhibitors," Proc Natl Acad Sci USA 109(36):14532-7 (2012).

[0006] 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 HIVassociated Kidney Disease by BRD4 Inhibition," J Biol Chem 287(34):8840-51 (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. Witherington, 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, glomerulonephritis, dermatomyositis, multiple sclerosis (Bandukwala, H.S., et al., "Selective inhibition of CD4+ T-cell cytokine production and autoimmunity by BET protein and c-Myc inhibitors," Proc Natl Acad Sci USA 109(36):14532-7 (2012)), scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, Type I diabetes(Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," Nat Rev Cancer 12(7):465-77 (2012)), septic shock (Zhang, G., et al., "Down-regulation of NF-kappaB Transcriptional Activity in HIVassociated Kidney Disease by BRD4 Inhibition," J Biol Chem 287(34):8840-51 (2012)), systemic lupus erythematosus (SLE) (Prinjha, R.K., J. Witherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains," Trends Pharmacol Sci 33(3):146-53 (2012)), rheumatoid arthritis (Denis, G.V., "Bromodomain coactivators in cancer, obesity, type 2 diabetes, and inflammation," Discov Med 10(55):489-99 (2010)), psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, uveitis, dry eye disease, scleroderma, mycosis fungoides, and Graves' disease.

[0007] 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, 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.

[0008] 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.

[0009] 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).

[0010] One aspect of the invention provides compounds, compositions, and methods for treating human cancer, including, but not limited to, cancers that result from aberrant translocation or overexpression of BET proteins (e.g., NUT midline carcinoma (NMC) (French, C.A., "NUT midline carcinoma," Cancer Genet Cytogenet 203(1):16-20 (2010) and B-cell lymphoma (Greenwald, R.J., et al., "E mu-BRD2 transgenic mice develop B-cell lymphoma and leukemia," Blood 103(4):1475-84 (2004)). NMC tumor cell growth is driven by a translocation of the Brd4 or Brd3 gene to the nutlin 1 gene. Filippakopoulos, P., et al., "Selective inhibition of BET bromodomains," Nature 468(7327):1067-73 (2010). BET inhibition has demonstrated potent antitumor activity in murine xenograft models of NMC, a rare but lethal form of cancer. The present disclosure provides a method for treating human cancers, including, but not limited to, cancers dependent on a member of the myc family of oncoproteins including c-myc, MYCN, and L-myc. Vita, M. and M. Henriksson, "The Myc oncoprotein as a therapeutic target for human cancer," Semin Cancer Biol 16(4):318-30 (2006). These cancers include Burkitt's lymphoma, acute myelogenous leukemia, multiple myeloma, and aggressive human medulloblastoma. Vita, M. and M. Henriksson, "The Myc oncoprotein as a therapeutic target for human cancer," Semin Cancer Biol 16(4):318-30 (2006). Cancers in which c-myc is overexpressed may be particularly susceptible to BET protein inhibition; it has been shown that treatment of tumors that have activation of c-myc with a BET inhibitor resulted in tumor regression through inactivation of c-myc transcription. 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); 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 bromodomains," Proc Natl Acad Sci USA 108(40):16669-74 (2011); Ott, C.J., et al., "BET bromodomain inhibition targets both c-Myc and IL7R in highrisk acute lymphoblastic leukemia," Blood 120(14):2843-52 (2012); Zuber, J., et al., "RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia," Nature 478(7370):524-8 (2011).

[0011] Embodiments of the invention include methods for treating human cancers that rely on BET proteins and pTEFb (Cdk9/CyclinT) to regulate oncogenes (Wang, S. and P.M. Fischer, "Cyclin-dependent kinase 9: a key transcriptional regulator and potential drug target in oncology, virology and cardiology," Trends Pharmacol Sci 29(6):302-13 (2008)), and cancers that can be treated by inducing apoptosis or senescence by inhibiting Bcl2, cyclin-dependent kinase 6 (CDK6) (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)), or human telomerase reverse transcriptase (hTERT) (Delmore, J.E., et al., "BET bromodomain inhibition as a therapeutic strategy to target c-Myc," Cell 146(6):904-17 (2010); Ruden, M. and N. Puri, "Novel anticancer therapeutics targeting telomerase," Cancer Treat Rev 39(5):444-456 (2012)).

[0012] Inhibition of BET proteins may also result in inhibition of enhancer and/or super-enhancer known to drive transcriptional programs associated with several human disease etiologies (Hnisz, D. et al. "Super-enhancers in the control of cell identity and disease," Cell 155:934-947 (2013); Loven, J. et al. "Selective inhibition of tumor oncogenes by disruption of super-enhancers." Cell 153: 320-334 (2013); Whyte, W.A. et al. "Master transcription factors and mediator establish super-enhancers at key cell identity genes," Cell 153:307-319 (2013)). The *MYC* oncogene is an example of a gene associated with a super enhancer that is disrupted by BET-bromodomain inhibitors. *See, e.g.,* Loven (2013). Thus, one aspect of the invention provides compounds, compositions, and methods for treating such diseases and disorders, including cancers associated with a super-enhancer or enhancer that may be disrupted with a BET inhibitor.

[0013] BET inhibitors may be useful in the treatment of cancers including, but not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia (*see*, *e.g.*, Loven (2013)), acute megakaryoblastic leukemia, acute monocytic leukemia, acute myeloid leukemia (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); Mertz, J.A., et al., "Targeting MYC dependence in cancer by inhibiting BET bromodomains," Proc Natl Acad Sci USA 108(40):16669-74 (2011); Zuber, J., et al., "RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia," Nature 478(7370):524-8 (2011)), adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma (Wu, X. et al. "Bromodomain and extraterminal (BET) protein inhibition suppresses human T cell leukemia virus 1 (HTLV-1) Tax protein-mediated tumorigenesis by inhibiting nuclear factor kappaB (NF-kappaB) signaling," J Biol Chem 288:36094-36105 (2013)), aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma (Knoechel, B. et al. "An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia," Nat Genet 46:364-370 (2014); Loosveld, M. et al. "Therapeutic Targeting of c-Myc in T-Cell Acute Lymphoblastic Leukemia (T-ALL)," Oncotarget 5(10):3168-72 (2014); Reynolds, C. et al. "Repression of BIM mediates survival signaling by MYC and AKT in high-risk T-cell acute lymphoblastic leukemia," Leukemia 28(9):1819-27 (2014); Roderick, J.E. et al. "c-Myc inhibition prevents leukemia initiation in mice and impairs the growth of relapsed and induction failure pediatric T-ALL cells," Blood 123:1040-1050 (2014)), angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell acute

lymphoblastic leukemia (Ott, C.J., et al., "BET bromodomain inhibition targets both c-Myc and IL7R in highrisk acute lymphoblastic leukemia," Blood 120(14):2843-52 (2012)), B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma (Greenwald, R.J., et al., "E mu-BRD2 transgenic mice develop B-cell lymphoma and leukemia," Blood 103(4):1475-84 (2004)), basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer (Lamoureux, F. et al. "Selective inhibition of BET bromodomain epigenetic signalling interferes with the bone-associated tumour vicious cycle," Nature Comm 5:3511 (2014), Brenner tumor, Brown tumor, Burkitt's lymphoma (Mertz, J.A., et al., "Targeting MYC dependence in cancer by inhibiting BET bromodomains," Proc Natl Acad Sci USA 108(40):16669-74 (2011)), breast cancer (Feng, Q. et al. "An epigenomic approach to therapy for tamoxifen-resistant breast cancer," Cell Res 24:809-819 (2014); Nagarajan, S. et al. "Bromodomain Protein BRD4 Is Required for Estrogen Receptor-Dependent Enhancer Activation and Gene Transcription," Cell Rep 8:460-469 (2014); Shi, J. et al. "Disrupting the Interaction of BRD4 with Diacetylated Twist Suppresses Tumorigenesis in Basal-like Breast Cancer," Cancer Cell 25:210-225 (2014)), brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma (Chapuy, B. et al. "Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma," Cancer Cell 24:777-790 (2013); Trabucco, S.E. et al. "Inhibition of bromodomain proteins for the treatment of human diffuse large B-cell lymphoma," Clin Can Res 21(1):113-122 (2015); Ceribelli, M. et al. "Blockade of oncogenic IkappaB kinase activity in diffuse large B-cell lymphoma by bromodomain and extraterminal domain protein inhibitors," PNAS 111:11365-11370 (2014)), dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme (Cheng, Z et al. "Inhibition of BET bromodomain targets genetically diverse glioblastoma," Clin Can Res 19:1748-1759 (2013); Pastori, C. et al. "BET bromodomain proteins are required for glioblastoma cell proliferation," Epigenetics 9:611-620 (2014)), glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (Lwin, T. et al. "A microenvironment-mediated c-Myc/miR-548m/HDAC6 amplification loop in non-Hodgkin B cell lymphomas," J Clin Invest 123:4612-4626 (2013)), invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, Leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia (Mertz, J.A., et al., "Targeting MYC dependence in cancer by inhibiting BET bromodomains," Proc Natl Acad Sci USA 108(40):16669-74 (2011)), chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer (Lockwood, W.W. et al. "Sensitivity of human lung adenocarcinoma cell lines to targeted inhibition of BET epigenetic signaling proteins," PNAS 109:19408-19413 (2012); Shimamura, T. et al. "Efficacy of BET bromodomain inhibition in Kras-mutant non-small cell lung cancer," Clin Can Res 19:6183-6192 (2013)) MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor (Baude, A. et al. "PRC2 loss amplifies Ras signaling in cancer," Nat Genet 46:1154-1155 (2014); Patel, A.J. et al. "BET bromodomain inhibition triggers apoptosis of NF1-associated malignant peripheral nerve sheath tumors through Bim induction," Cell Rep 6:81-92 (2014)), malignant triton tumor, mantle cell lymphoma (Moros, A. et al. "Synergistic antitumor activity of lenalidomide with the BET bromodomain inhibitor CPI203 in bortezomib-resistant mantle cell lymphoma," Leukemia 28:2049-2059 (2014)), marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma (Bandopadhayay, P. et al. "BET bromodomain inhibition of MYC-amplified medulloblastoma," Clin Can Res 20:912-925 (2014); Henssen, A.G. et al. "BET bromodomain protein inhibition is a therapeutic option for medulloblastoma" Oncotarget 4(11):2080-2089 (2013); Long, J. et al. "The BET bromodomain inhibitor I-BET151 acts downstream of Smoothened to abrogate the growth of Hedgehog driven cancers," J Biol Chem 289(51):35494-35502 (2014); Tang, Y. et al. "Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition," Nat Med 20(7):732-40 (2014); Venataraman, S. et al. "Inhibition of BRD4 attenuates tumor cell self-renewal and suppresses stem cell signaling in MYC driven medulloblastoma," Oncotarget 5(9):2355-71 (2014)) melanoma (Segura et al, "BRD4 is a novel therapeutic target in melanoma," Cancer Res 72(8):Supplement 1 (2012)), meningioma, Merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mixed lineage leukemia (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)), mucinous tumor, multiple myeloma (Delmore, J.E., et al., "BET bromodomain inhibition as a therapeutic strategy to target c-Myc," Cell 146(6):904-17 (2010)), muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma (Puissant, A. et al. "Targeting MYCN in neuroblastoma by BET bromodomain inhibition," Cancer Discov 3:308-323 (2013); Wyce, A. et al. "BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models," PLoS One 8:e72967 (2014)), neurofibroma, neuroma, nodular melanoma, NUT-midline

carcinoma (Filippakopoulos, P., et al., "Selective inhibition of BET bromodomains," Nature 468(7327):1067-73 (2010)), ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma (Lamoureux, F. et al. "Selective inhibition of BET bromodomain epigenetic signalling interferes with the bone-associated tumour vicious cycle" Nat Commun 5:3511 (2014); Lee, D.H. et al. "Synergistic effect of JQ1 and rapamycin for treatment of human osteosarcoma," Int J Cancer 136(9):2055-2064 (2014)), ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma (Tolani, B. et al. "Targeting Myc in KSHV-associated primary effusion lymphoma with BET bromodomain inhibitors," Oncogene 33:2928-2937 (2014)), primary peritoneal cancer, prostate cancer (Asangani, I.A. et al. "Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer," Nature 510:278-282 (2014); Cho, H. et al. "RapidCaP, a novel GEM model for metastatic prostate cancer analysis and therapy, reveals myc as a driver of Pten-mutant metastasis," Cancer Discov 4:318-333 (2014); Gao, L. et al. "Androgen receptor promotes ligand-independent prostate cancer progression through c-Myc upregulation," PLoS One 8:e63563 (2013): Wyce, A. et al. "Inhibition of BET bromodomain proteins as a therapeutic approach in prostate cancer," Oncotarget 4:2419-2429 (2013)), pancreatic cancer (Sahai, V. et al. "BET bromodomain inhibitors block growth of pancreatic cancer cells in three-dimensional collagen," Mol Cancer Ther 13:1907-1917 (2014)), pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor. Thus, one aspect of the inventions provides compounds, compositions, and methods for treating such cancers.

[0014] BET inhibitors of the invention may be useful in the treatment of cancers that are resistant to current and future cancer treatments, as BET proteins are involved in the mechanisms of resistance of several anti-cancer treatment, including chemotherapy (Feng, Q., et al. "An epigenomic approach to therapy for tamoxifen-resistant breast cancer" Cell Res 24:809-819 (2014)), immunotherapy (Emadali, A., et al. "Identification of a novel BET bromodomain inhibitor-sensitive, gene regulatory circuit that controls Rituximab response and tumour growth in aggressive lymphoid cancers," EMBO Mol Med 5:1180-1195 (2013))., hormone-deprivation therapies (Asangani, I.A. et al. "Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer," Nature 510:278-282 (2014)), or other molecules ((Knoechel, B. et al. "An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia," Nat Genet 46:364-370 (2014)). In these instances, the BET proteins are involved in the resistance mechanism to the cancer therapy, and treatment with a BET inhibitor could either restore sensitivity to the treatment, inhibit proliferation or induce cell death or senescence, either alone or in combination with other therapies (Moros, A. et al. "Synergistic antitumor activity of lenalidomide with the BET bromodomain inhibitor CPI203 in bortezomib-resistant mantle cell lymphoma," Leukemia 28:2049-2059 (2014)).

[0015] 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 183(2):470-479 (2013). Thus, one aspect of the invention provides compounds, compositions, and methods for treating such benign proliferative and fibrotic disorders.

[0016] Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the United States. Roger, V.L., et al., "Heart disease and stroke statistics--2012 update: a report from the American Heart Association," Circulation 125(1):e2-e220 (2012). Atherosclerosis, an underlying cause of CVD, is a multifactorial disease characterized by dyslipidemia and inflammation. BET inhibitors are expected to be efficacious in atherosclerosis and associated conditions because of aforementioned anti-inflammatory effects as well as ability to increase transcription of ApoA-I, the major constituent of HDL. Mirguet, O., et al., "From ApoA1 upregulation to BET family bromodomain inhibition: discovery of I-BET151," Bioorg Med Chem Lett 22(8):2963-7 (2012); Chung, C.W., et al., "Discovery and characterization of small molecule inhibitors of the BET family bromodomains," J Med Chem 54(11):3827-38 (2011). Accordingly, one aspect of the invention provides compounds, compositions, and methods for treating cardiovascular disease, including but not limited to atherosclerosis.

[0017] Up-regulation of ApoA-I is considered to be a useful strategy in treatment of atherosclerosis and CVD. Degoma,

E.M. and D.J. Rader, "Novel HDL-directed pharmacotherapeutic strategies," Nat Rev Cardiol 8(5):266-77 (2011). BET inhibitors have been shown to increase ApoA-I transcription and protein expression. Mirguet, O., et al., "From ApoA1 upregulation to BET family bromodomain inhibition: discovery of I-BET151," Bioorg Med Chem Lett 22(8):2963-7 (2012); Chung, C.W., et al., "Discovery and characterization of small molecule inhibitors of the BET family bromodomains," J Med Chem 54(11):3827-38 (2011). It has also been shown that BET inhibitors bind directly to BET proteins and inhibit their binding to acetylated histones at the ApoA-1 promoter, suggesting the presence of a BET protein repression complex on the ApoA-1 promoter, which can be functionally disrupted by BET inhibitors. It follows that, BET inhibitors may be useful in the treatment of disorders of lipid metabolism via the regulation of ApoA-I and HDL such as hypercholesterolemia, dyslipidemia, atherosclerosis (Degoma, E.M. and D.J. Rader, "Novel HDL-directed pharmacotherapeutic strategies," Nat Rev Cardiol 8(5):266-77 (2011)), and Alzheimer's disease and other neurological disorders. Elliott, D.A., et al., "Apolipoproteins in the brain: implications for neurological and psychiatric disorders," Clin Lipidol 51(4):555-573 (2010). Thus, one aspect of the invention provides compounds, compositions, and methods for treating cardiovascular disorders by upregulation of ApoA-1.

[0018] 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.

[0019] Obesity-associated inflammation is a hallmark of type II diabetes, insulin resistance, and other metabolic disorders. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," Nat Rev Cancer 12(7):465-77 (2012); Denis, G.V., "Bromodomain coactivators in cancer, obesity, type 2 diabetes, and inflammation," Discov Med 10(55):489-99 (2010). Consistent with the ability of BET inhibitors to inhibit inflammation, gene disruption of Brd2 in mice ablates inflammation and protects animals from obesity-induced insulin resistance. Wang, F., et al., "Brd2 disruption in mice causes severe obesity without Type 2 diabetes," Biochem J 425(1):71-83 (2010). It has been shown that Brd2 interacts with PPAPγ and opposes its transcriptional function. Knockdown of Brd2 *in vitro* promotes transcription of PPARγ-regulated networks, including those controlling adipogenesis. Denis, G.V., et al, "An emerging role for bromodomain-containing proteins in chromatin regulation and transcriptional control of adipogenesis," FEBS Lett 584(15):3260-8 (2010). In addition Brd2 is highly expressed in pancreatic β-cells and regulates proliferation and insulin transcription. Wang, F., et al., "Brd2 disruption in mice causes severe obesity without Type 2 diabetes," Biochem J 425(1):71-83 (2010). Taken together, the combined effects of BET inhibitors on inflammation and metabolism decrease insulin resistance and may be useful in the treatment of pre-diabetic and type II diabetic individuals as well as patients with other metabolic complications. Belkina, A.C. and G.V. Denis, "BET domain co-regulators in obesity, inflammation and cancer," Nat Rev Cancer 12(7):465-77 (2012). Accordingly, one aspect of the invention provides compounds, compositions, and methods for treatment and prevention of metabolic disorders, including but not limited to obesity-associated inflammation, type II diabetes, and insulin resistance.

[0020] 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. Host-encoded BET proteins have been shown to be important for transcriptional activation and repression of viral promoters. Brd4 interacts with the E2 protein of human papilloma virus (HPV) to enable E2 mediated transcription of E2-target genes. Gagnon, D., et al., "Proteasomal degradation of the papillomavirus E2 protein is inhibited by overexpression of bromodomain-containing protein 4," J Virol 83(9):4127-39 (2009). Similarly, Brd2, Brd3, and Brd4 all bind to latent nuclear antigen 1 (LANA1), encoded by Kaposi's sarcoma-associated herpes virus (KSHV), promoting LANA1-dependent proliferation of KSHV-infected cells. You, J., et al., "Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen interacts with bromodomain protein Brd4 on host mitotic chromosomes," J Virol 80(18):8909-19 (2006). A BET inhibitor has been shown to inhibit the Brd4-mediated recruitment of the transcription elongation complex pTEFb to the Epstein-Barr virus (EBV) viral C promoter, suggesting therapeutic value for EBV-associated malignancies. Palermo, R.D., et al., "RNA polymerase II stalling promotes nucleosome occlusion and pTEFb recruitment to drive immortalization by Epstein-Barr virus," PLoS Pathog 7(10):e1002334 (2011). Also, a BET inhibitor reactivated HIV in models of latent T cell infection and latent monocyte infection, potentially allowing for viral eradication by complementary anti-retroviral therapy. Zhu, J., et al., "Reactivation of Latent HIV-1 by Inhibition of BRD4," Cell Rep 2(4):807-816 (2012); Banerjee, C., et al., "BET bromodomain inhibition as a novel strategy for reactivation of HIV-1," J Leukoc Biol 92(6):1147-1154 (2012); Bartholomeeusen, K., et al., "BET bromodomain inhibition activates transcription via a transient release of P-TEFb from 7SK snRNP," J Biol Chem 287(43):36609-36616 (2012); Li, Z., et al., "The BET bromodomain inhibitor JQ1 activates HIV latency through antagonizing Brd4 inhibition of Tat-transactivation," Nucleic Acids Res (2012). Thus, the invention also provides compounds,

compositions, and methods for treatment and prevention of episome-based DNA virus infections. In particular, one aspect of the invention provides compounds, compositions, and methods for treatment and/or prevention of a viral infection, including, but not limited to infection by HPV, KSHV, EBV, HIV, HBV, HCV, adenovirus, poxvirus herpes virus, or a malignancy associated with that infection.

[0021] Some central nervous system (CNS) diseases are characterized by disorders in epigenetic processes. Brd2 haplo-insufficiency has been linked to neuronal deficits and epilepsy. Velisek, L., et al., "GABAergic neuron deficit as an idiopathic generalized epilepsy mechanism: the role of BRD2 haploinsufficiency in juvenile myoclonic epilepsy," PLoS One 6(8): e23656 (2011). SNPs in various bromodomain-containing proteins have also been linked to mental disorders including schizophrenia and bipolar disorders. Prinjha, R.K., J. Witherington, and K. Lee, "Place your BETs: the therapeutic potential of bromodomains," Trends Pharmacol Sci 33(3):146-53 (2012). In addition, the ability of BET inhibitors to increase ApoA-I transcription may make BET inhibitors useful in Alzheimer's disease therapy considering the suggested relationship between increased ApoA-I and Alzheimer's disease and other neurological disorders. Elliott, D.A., et al., "Apolipoproteins in the brain: implications for neurological and psychiatric disorders," Clin Lipidol 51(4):555-573 (2010). Accordingly, one aspect of the invention provides compounds, compositions, and methods for treating such CNS diseases and disorders.

[0022] BRDT is the testis-specific member of the BET protein family which is essential for chromatin remodeling during spermatogenesis. Gaucher, J., et al., "Bromodomain-dependent stage-specific male genome programming by Brdt," EMBO J 31(19):3809-20 (2012); Shang, E., et al., "The first bromodomain of Brdt, a testis-specific member of the BET sub-family of double-bromodomain-containing proteins, is essential for male germ cell differentiation," Development 134(19):3507-15 (2007). Genetic depletion of BRDT or inhibition of BRDT interaction with acetylated histones by a BET inhibitor resulted in a contraceptive effect in mice, which was reversible when small molecule BET inhibitors were used. Matzuk, M.M., et al., "Small-Molecule Inhibition of BRDT for Male Contraception," Cell 150(4):673-684 (2012); Berkovits, B.D., et al., "The testis-specific double bromodomain-containing protein BRDT forms a complex with multiple spliceosome components and is required for mRNA splicing and 3'-UTR truncation in round spermatids," Nucleic Acids Res 40(15):7162-75 (2012). These data suggest potential utility of BET inhibitors as a novel and efficacious approach to male contraception. Thus, another aspect of the invention provides compounds, compositions, and methods for male contraception.

[0023] Monocyte chemotactic protein-1 (MCP-1, CCL2) plays an important role in cardiovascular disease. Niu, J. and P.E. Kolattukudy, "Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications," Clin Sci (Lond) 117(3):95-109 (2009). MCP-1, by its chemotactic activity, regulates recruitment of monocytes from the arterial lumen to the subendothelial space, where they develop into macrophage foam cells, and initiate the formation of fatty streaks which can develop into atherosclerotic plaque. Dawson, J., et al., "Targeting monocyte chemoattractant protein-1 signalling in disease," Expert Opin Ther Targets 7(1):35-48 (2003). The critical role of MCP-1 (and its cognate receptor CCR2) in the development of atherosclerosis has been examined in various transgenic and knockout mouse models on a hyperlipidemic background. Boring, L., et al., "Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis," Nature 394(6696):894-7 (1998); Gosling, J., et al., "MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B," J Clin Invest 103(6):773-8 (1999); Gu, L., et al., "Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice," Mol Cell 2(2):275-81 (1998); Aiello, R.J., et al., "Monocyte chemoattractant protein-1 accelerates atherosclerosis in apolipoprotein E-deficient mice," Arterioscler Thromb Vasc Biol 19(6):1518-25 (1999). These reports demonstrate that abrogation of MCP-1 signaling results in decreased macrophage infiltration to the arterial wall and decreased atherosclerotic lesion development.

[0024] The association between MCP-1 and cardiovascular disease in humans is well-established. Niu, J. and P.E. Kolattukudy, "Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications," Clin Sci (Lond) 117(3):95-109 (2009). MCP-1 and its receptor are overexpressed by endothelial cells, smooth muscle cells, and infiltrating monocytes/macrophages in human atherosclerotic plaque. Nelken, N.A., et al., "Monocyte chemoattractant protein-1 in human atheromatous plaques," J Clin Invest 88(4):1121-7 (1991). Moreover, elevated circulating levels of MCP-1 are positively correlated with most cardiovascular risk factors, measures of coronary atherosclerosis burden, and the incidence of coronary heart disease (CHD). Deo, R., et al., "Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis," J Am Coll Cardiol 44(9):1812-8 (2004). CHD patients with among the highest levels of MCP-1 are those with acute coronary syndrome (ACS). de Lemos, J.A., et al., "Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes," Circulation 107(5):690-5 (2003). In addition to playing a role in the underlying inflammation associated with CHD, MCP-1 has been shown to be involved in plaque rupture, ischemic/reperfusion injury, restenosis, and heart transplant rejection. Niu, J. and P.E. Kolattukudy, "Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications," Clin Sci (Lond) 117(3):95-109 (2009).

[0025] MCP-1 also promotes tissue inflammation associated with autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (MS). MCP-1 plays a role in the infiltration of macrophages and lymphocytes into the joint

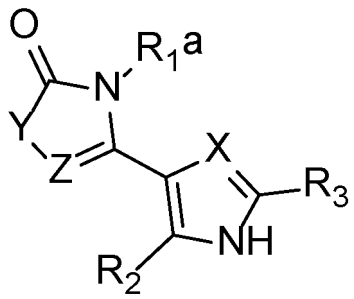
in RA, and is overexpressed in the synovial fluid of RA patients. Koch, A.E., et al., "Enhanced production of monocyte chemoattractant protein-1 in rheumatoid arthritis," J Clin Invest 90(3):772-9 (1992). Blockade of MCP-1 and MCP-1 signaling in animal models of RA have also shown the importance of MCP-1 to macrophage accumulation and proinflammatory cytokine expression associated with RA. Brodmerkel, C.M., et al., "Discovery and pharmacological characterization of a novel rodent-active CCR2 antagonist, INCB3344," J Immunol 175(8):5370-8 (2005); Bruhl, H., et al., "Dual role of CCR2 during initiation and progression of collagen-induced arthritis: evidence for regulatory activity of CCR2+ T cells," J Immunol 172(2):890-8 (2004); Gong, J.H., et al., "An antagonist of monocyte chemoattractant protein 1 (MCP-1) inhibits arthritis in the MRL-lpr mouse model," J Exp Med 186(1):131-7 (1997); 65. Gong, J.H., et al., "Post-onset inhibition of murine arthritis using combined chemokine antagonist therapy," Rheumatology (Oxford 43(1): 39-42 (2004).

[0026] Overexpression of MCP-1, in the brain, cerebrospinal fluid (CSF), and blood, has also been associated with chronic and acute MS in humans. Mahad, D.J. and R.M. Ransohoff, "The role of MCP-1 (CCL2) and CCR2 in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE)," Semin Immunol 15(1):23-32 (2003). MCP-1 is overexpressed by a variety of cell types in the brain during disease progression and contributes to the infiltration of macrophages and lymphocytes which mediate the tissue damage associated with MS. Genetic depletion of MCP-1 or CCR2 in the experimental autoimmune encephalomyelitis (EAE) mouse model, a model resembling human MS, results in resistance to disease, primarily because of decreased macrophage infiltration to the CNS. Fife, B.T., et al., "CC chemokine receptor 2 is critical for induction of experimental autoimmune encephalomyelitis," J Exp Med 192(6):899-905 (2000); Huang, D.R., et al., "Absence of monocyte chemoattractant protein 1 in mice leads to decreased local macrophage recruitment and antigen-specific T helper cell type 1 immune response in experimental autoimmune encephalomyelitis," J Exp Med 193(6):713-26 (2001).

[0027] Preclinical data have suggested that small- and large-molecule inhibitors of MCP-1 and CCR2 have potential as therapeutic 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.

[0028] 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.

[0029] The broadest disclosure relates to compounds of Formula I and methods of administering a therapeutically effective amount of those compounds to a mammal (e.g., a human) in need thereof:



Formula I

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

X is selected from CH and N;
Y is selected from -NH, -NR_{1b} and oxygen;
Z is selected from N, and -CH-;
$\mathbf{R_{1a}}$ and $\mathbf{R_{1b}}$ are independently selected from alkyl (C_1-C_6), carbocycle (C_3-C_{10}), heterocycle (C_2-C_{10}) optionally substituted with 1 to 3 groups selected from R_4;
$\mathbf{R_2}$ is selected from aryl (C_5-C_{10}) and heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
$\mathbf{R_3}$ is selected from carbocycle (C_3-C_{10}) and heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), cycloalkyl (C_3-C_8) (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl); alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as - NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NHMe, -$C(O)NEt_2$, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, - SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt,

-SPr, -SBu), -COOH, and ester (such as - C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and
each $\mathbf{R_5}$ is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, - C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as-SO_2Me, -SO_2Et, -SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0030] In another aspect of the invention, a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, diluents or excipients is provided.

[0031] In yet another aspect of the invention there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof for use in therapy, in particular in the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

[0032] In yet another aspect of the invention there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

Definitions

[0033] 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.

[0034] 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, hyperbetalipoproteinemia, 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.

[0035] 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.

[0036] 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 (PML), non-Hodgkin's lymphoma, neuroblastoma, medulloblastoma, lung carcinoma (NSCLC, SCLC), and colon carcinoma.

[0037] "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.

[0038] 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.

[0039] As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder.

[0040] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -$CONH_2$ is attached through the carbon atom.

[0041] 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 is 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 impractical, synthetically non-feasible and/or inherently unstable.

[0042] As used herein, the term "hydrate" refers to a crystal form with either a stoichiometric or non-stoichiometric amount of water is incorporated into the crystal structure.

[0043] 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 (C_2-C_8)alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, and 4-(2-methyl-3-butene)-pentenyl.

[0044] The term "alkoxy" as used herein refers to an alkyl group attached to an oxygen (-O-alkyl-). "Alkoxy" groups also include an alkenyl group attached to an oxygen ("alkenyloxy") or an alkynyl group attached to an oxygen ("alkynyloxy") 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 (C_1-C_8)alkoxy. Exemplary alkoxy groups include, but are not limited to methoxy and ethoxy.

[0045] 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 (C_1-C_8)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.

[0046] 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-butyl-2-hexynyl.

[0047] The term "amide" as used herein refers to the form -$NR_aC(O)(R_b)$- or -$C(O)NR_bR_c$, wherein R_a, R_b and R_c are each independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, 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_b 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, carbamic 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).

[0048] The term "amine" or "amino" as used herein refers to the form -NR_dR_e or -$N(R_d)R_e$-, where R_d and R_e are independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, carbamate, cycloalkyl, haloalkyl, heteroaryl, heterocycle, 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 piperidinyl). 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 Rd and Re each may be optionally substituted with hydroxyl, halogen, alkoxy, ester, or amino.

[0049] 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 heterocyclyls. The aryl groups of this present disclosure can be substituted with groups selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide, and thioketone. Exemplary aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, 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

"(C_6)aryl."

[0050] The term "arylalkyl" as used herein refers to an alkyl group having at least one aryl substituent (e.g., -aryl-alkyl-). Exemplary arylalkyl 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 "(C_6)arylalkyl."

[0051] The term "carbamate" as used herein refers to the form -R_gOC(O)N(R_h)-, -R_gOC(O)N(R_h)R_i-, or -OC(O)N$R_h$$R_i$, wherein R_g, R_h and R_i are each independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, and hydrogen. Exemplary carbamates include, but are not limited to, arylcarbamates or heteroaryl carbamates (e.g., wherein at least one of R_g, R_h and R_i are independently selected from aryl or heteroaryl, such as pyridine, pyridazine, pyrimidine, and pyrazine).

[0052] The term "carbocycle" as used herein refers to an aryl or cycloalkyl group.

[0053] 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 carbonyl group, e.g., -C(O)-COOH or salts, such as -C(O)-COONa.

[0054] The term "cyano" as used herein refers to -CN.

[0055] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen.

[0056] 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 "(C_3-C_8)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 alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Cycloalkyl groups can be fused to other cycloalkyl saturated or unsaturated, aryl, or heterocyclyl groups.

[0057] 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 alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, 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).

[0058] The term "ester" refers to the structure -C(O)O-, -C(O)O-R_j-, -R_kC(O)O-R_j-, or -R_kC(O)O-, where O 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 heterocyclyl. R_k can be a hydrogen atom, but R_j cannot be a hydrogen atom. 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 Rj or Rk is alkyl, such as -O-C(O)-alkyl, -C(O)-O-alkyl-, and -alkyl-C(O)-O-alkyl-. Exemplary esters also include aryl or heteoraryl esters, e.g. wherein at least one of Rj or Rk is a heteroaryl group such as pyridine, pyridazine, pyrimidine and pyrazine, such as a nicotinate ester. Exemplary esters also include reverse esters having the structure -R_kC(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.

[0059] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[0060] The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms. "Haloalkyls" also encompass alkenyl or alkynyl groups substituted with one or more halogen atoms.

[0061] 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, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, 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, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidilyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, and oxazolyl. 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."

[0062] The terms "heterocycle," "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 (heteroaryls) or non-aromatic. Heterocycles can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy,

cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, 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, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, thiopyranyl, and triazolyl.

[0063] The terms "hydroxy" and "hydroxyl" as used herein refer to -OH.

[0064] The term "hydroxyalkyl" as used herein refers to a hydroxy attached to an alkyl group.

[0065] The term "hydroxyaryl" as used herein refers to a hydroxy attached to an aryl group.

[0066] The term "ketone" as used herein refers to the structure -C(O)-Rn (such as acetyl, $-C(O)CH_3$) or $-R_n-C(O)-R_o-$. The ketone can be attached to another group through R_n or R_o. R_n or R_o can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl or aryl, or R_n or R_o can be joined to form a 3- to 12-membered ring.

[0067] The term "monoester" as used herein refers to an analogue of a dicarboxylic acid wherein one of the carboxylic acids is functionalized as an ester and the other carboxylic acid is a free carboxylic acid or salt of a carboxylic acid. Examples of monoesters include, but are not limited to, to monoesters of succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, oxalic and maleic acid.

[0068] 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, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone.

[0069] The term "thioalkyl" as used herein refers to an alkyl group attached to a sulfur (-S-alkyl-).

[0070] "Alkyl," "alkenyl," "alkynyl", "alkoxy", "amino" and "amide" groups can be optionally substituted with or interrupted by or branched with at least one group selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carbonyl, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide, thioketone, ureido and N. The substituents may be branched to form a substituted or unsubstituted heterocycle or cycloalkyl.

[0071] 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_{1-8} alkyl, alkenyl or alkynyl; C_{1-6} aryl, C_{2-5} heteroaryl; C_{37} cycloalkyl; C_{1-8} alkoxy; C_6 aryloxy; -CN; -OH; oxo; halo, carboxy; amino, such as $-NH(C_{1-8}$ alkyl), $-N(C_{1-8}$ alkyl$)_2$, $-NH((C_6)$aryl), or $-N((C_6)$aryl$)_2$; formyl; ketones, such as $-CO(C_{1-8}$ alkyl), $-CO((C_6$ aryl) esters, such as $-CO_2(C_{1-8}$ alkyl) and $-CO_2$ (C_6 aryl). One of skill in art can readily choose a suitable substitution based on the stability and pharmacological and synthetic activity of the compound of the present disclosure.

[0072] 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.

[0073] 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.

[0074] 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 of the present disclosure. A discussion is provided in Higuchi et al., "Prodrugs as Novel Delivery Systems," ACS Symposium Series, Vol. 14, and in Roche, E.B., ed. Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0075] 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,

gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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."

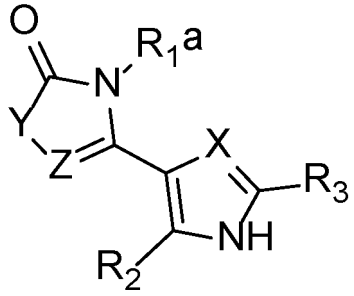
[0080] The compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the present disclosure, even though only one tautomeric structure is depicted.

Exemplary Embodiments of the Invention

[0081] It is to be understood that the invention is defined only by the appended claims. The embodiments of the description are only illustrative by nature.

[0082] Certain embodiments of the disclosure provide compounds of Formula I, which include compounds of Formula Ia, compositions and formulations containing such compounds, and methods of using and making such compounds.

[0083] Some embodiments relate to a compound according to Formula I:

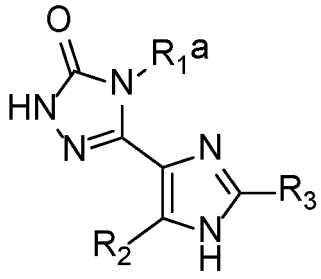


Formula I

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

X is selected from CH and N;
Y is selected from -NH, -N-R_{1b} and oxygen;
Z is selected from N, and -CH-;
$\mathbf{R_{1a}}$ and $\mathbf{R_{1b}}$ are independently selected from alkyl (C_1-C_6), carbocycle (C_3-C_{10}), and heterocycle (C_2-C_{10}) optionally substituted with 1 to 3 groups selected from R_4;
$\mathbf{R_2}$ is selected from aryl (C_5-C_{10}) and heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
$\mathbf{R_3}$ is selected from carbocycle (C_3-C_{10}) and heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), cycloalkyl (C_3-C_8) (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as-NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, - SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as - C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and
each $\mathbf{R_5}$ is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy(C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, - C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as-SO_2Me, -SO_2Et, -SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0084] Some embodiments provide compound of Formula Ia, which are a subset of compounds of Formula I, compositions and formulations containing such compounds, and methods of using and making such compounds:



Formula Ia

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

$\mathbf{R_{1a}}$ is selected from alkyl (C_1-C_6), carbocycle (C_3-C_{10}), and heterocycle (C_2-C_{10}) optionally substituted with 1 to 3 groups selected from R_4;

$\mathbf{R_2}$ is selected from aryl (C_5-C_{10}) and heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;

$\mathbf{R_3}$ is selected from carbocycle (C_3-C_{10}) and heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;

each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), cycloalkyl (C_3-C_8) (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as-NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, -C(O)NHMe, - C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, - SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as - C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and

each **R_5** is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (C_1-C_6) (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as - SO_2Me, -SO_2Et, -SO_2Pr), thio-alkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

[0085] In some embodiments, each **R_4** in Formula I or Formula Ia is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, - NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, -SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu), each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_3, and R_5 are as defined in paragraphs 83 or 84.

[0086] In some embodiments according to Formula I, X is N; and Y, Z, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0087] In some embodiments according to Formula I, X is CH; and Y, Z, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0088] In some embodiments according to Formula I, Y is -NR_{1b}; and X, Z, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0089] In some embodiments according to Formula I, Y is -NH; and X, Z, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0090] In some embodiments according to Formula I, Y is oxygen; and X, Z, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

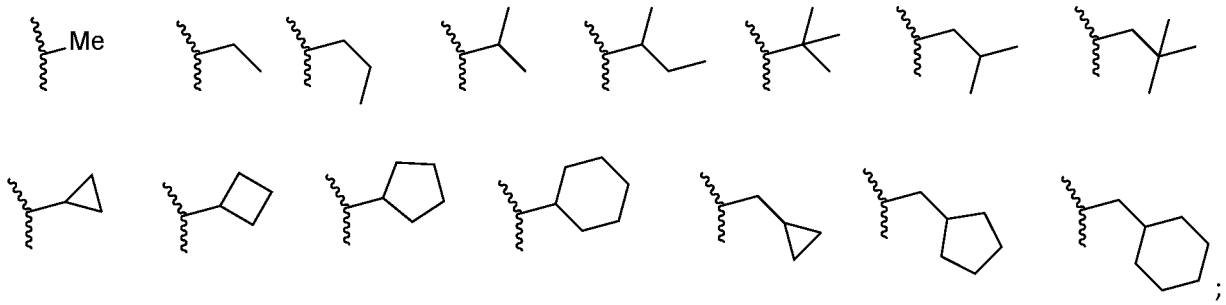
[0091] In some embodiments according to Formula I, Z is N; and X, Y, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0092] In some embodiments according to Formula I, Z is CH; and X, Y, R_{1a}, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0093] In some embodiments according to Formula I or Formula Ia, R_{1a} is selected from alkyl (C_1-C_6), carbocycle (C_3-C_6), heterocycle (C_2-C_5) optionally substituted with 1 to 3 groups selected from R_4; and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

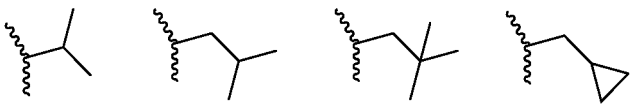
[0094] In some embodiments according to Formula I or Formula Ia, R_{1a} is selected from alkyl (C_1-C_6) and carbocycle (C_3-C_6) optionally substituted with 1 to 3 groups selected from R_4; and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

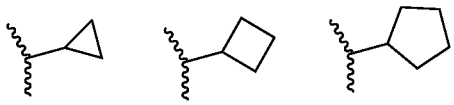
[0095] In some embodiments according to Formula I or Formula Ia, R_{1a} is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:



and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0096] In some embodiments according to Formula I of Formula Ia, R_{1a} is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:

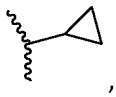




;

and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

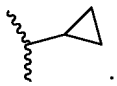
[0097] In some embodiments according to Formula I or Formula Ia, R_{1a} is



,

which may be optionally substituted with 1 to 3 groups selected from R_4; and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

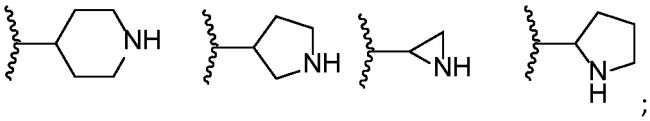
[0098] In some embodiments according to Formula I or Formula Ia, R_{1a} is



;

and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0099] In some embodiments according to Formula I or Formula Ia, R_{1a} is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:



;

and X, Y, Z, R_{1b}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-156 herein.

[0100] In some embodiments according to Formula I, R_{1b} is selected from alkyl (C_1-C_6); and X, Y, Z, R_{1a}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0101] In some embodiments according to Formula I, R_{1b} is selected from methyl and ethyl; and X, Y, Z, R_{1a}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

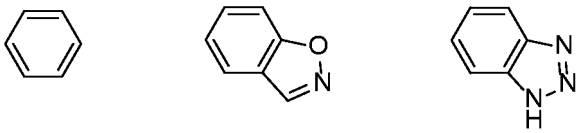
[0102] In some embodiments according to Formula I, R_{1b} is methyl; and X, Y, Z, R_{1a}, R_2, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

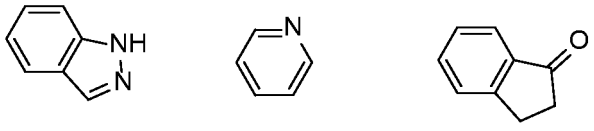
[0103] In some embodiments according to Formula I or Formula Ia, R_2 is selected from optionally substituted bicyclic aryl and bicyclic heteroaryl groups; and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0104] In some embodiments according to Formula I or Formula Ia, R_2 is selected from aryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0105] In some embodiments according to Formula I or Formula Ia, R_2 is selected from heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0106] In some embodiments according to Formula I or Formula Ia, R_2 is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:

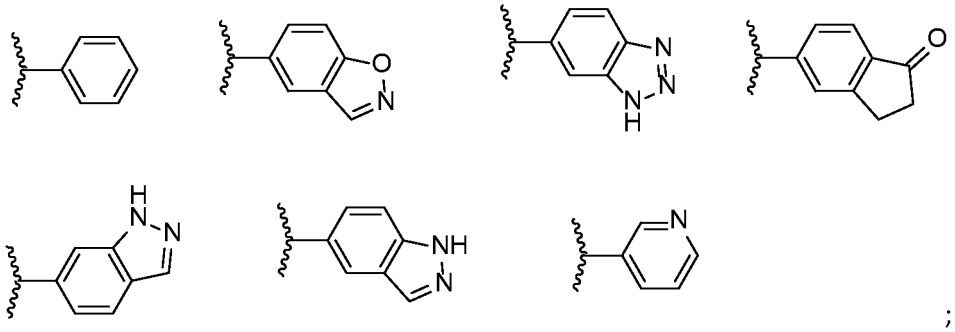




;

and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

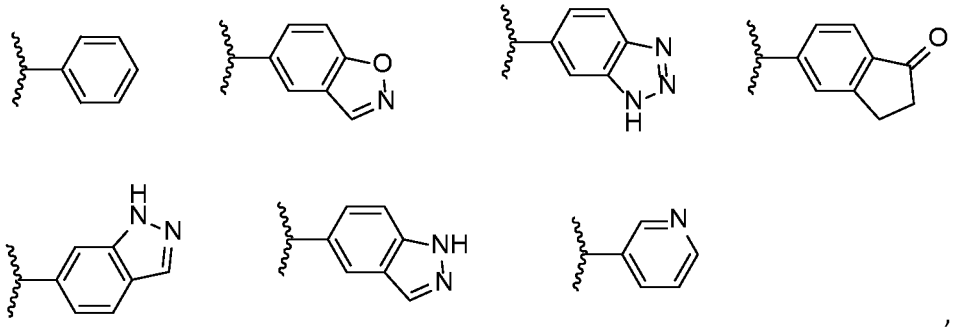
[0107] In some embodiments according to Formula I or Formula Ia, R_2 is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



;

and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

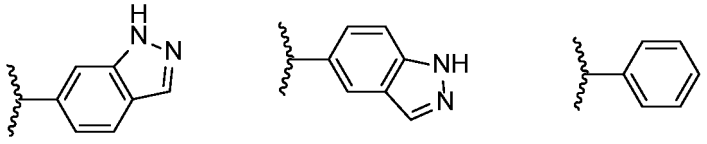
[0108] In some embodiments according to Formula I or Formula Ia, R_2 is selected from, but not limited to, the following structures:



,

which may be optionally substituted with 1 to 2 groups selected from alkyl (C_1-C_6), halogen, ketone, amide, and ester; and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

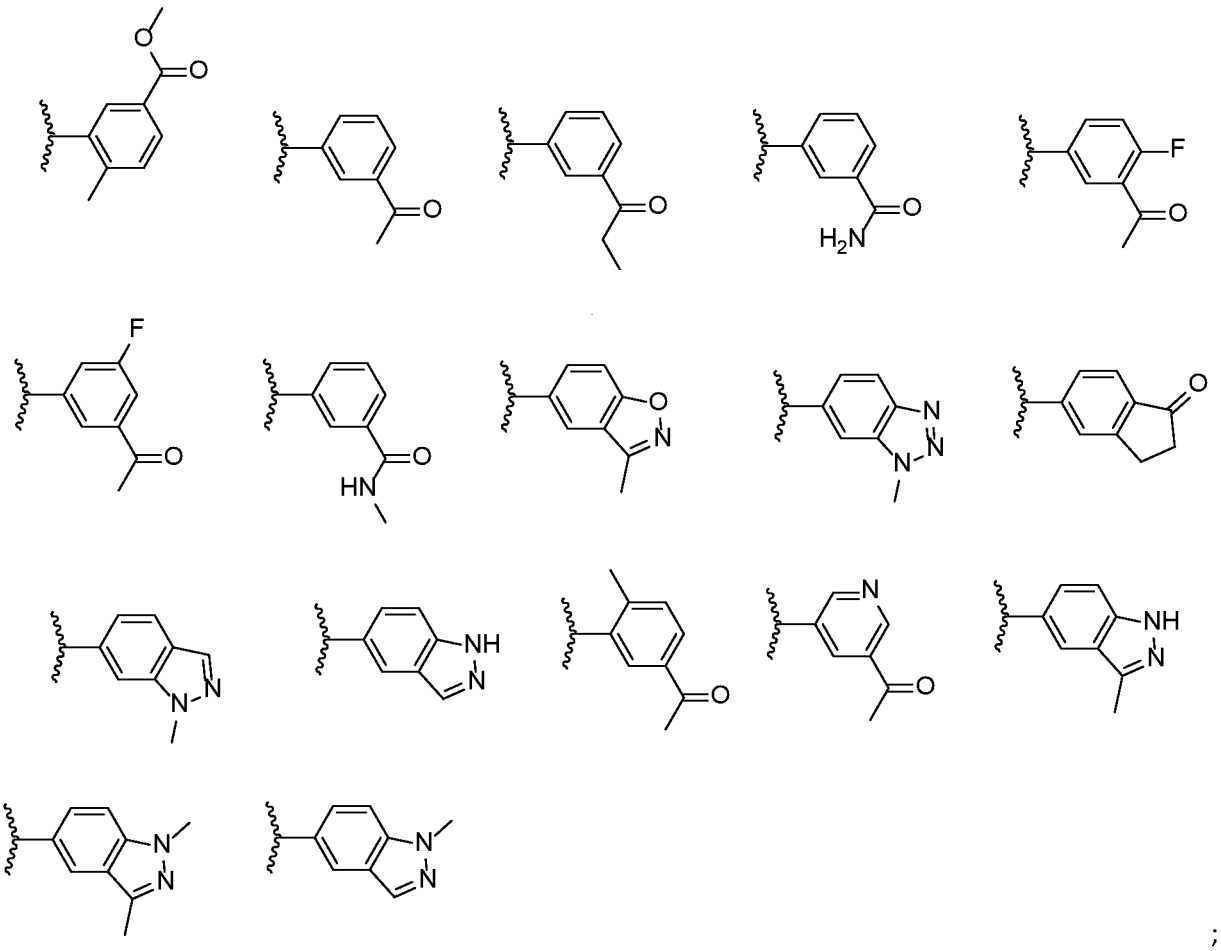
[0109] In some embodiments according to Formula I or Formula Ia, R_2 is selected from, but not limited to, the following structures:



,

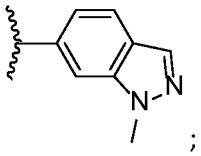
which may be optionally substituted with 1 to 2 groups selected from alkyl (C_1-C_6), halogen, ketone, amide, and ester; and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0110] In some embodiments according to Formula I or Formula Ia, R_2 is selected from, but not limited to, the following structures:



and X, Y, Z, R_{1a}, R_{1b}, R_3, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0111] In some embodiments according to Formula I or Formula Ia, R_2 is



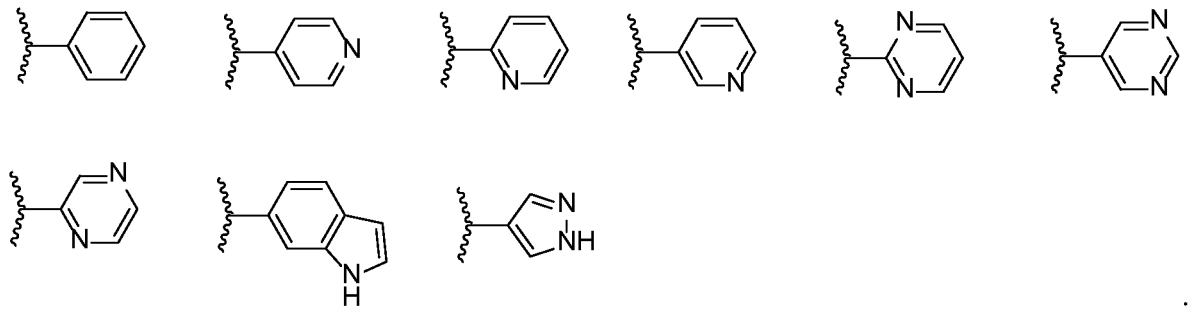
and X, Y, Z, R_{1a}, R_{1b}, R_3, and R_4 are as defined in any one or combination of paragraphs 83-124 herein.

[0112] In some embodiments according to Formula I or Formula Ia, R_3 is selected from carbocycle (C_3-C_{10}) optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0113] In some embodiments according to Formula I or Formula Ia, R_3 is selected from aryl groups (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

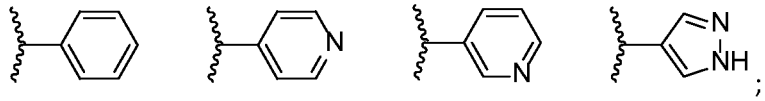
[0114] In some embodiments according to Formula I or Formula Ia, R_3 is selected from heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0115] In some embodiments according to Formula I or Formula Ia, R_3 is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



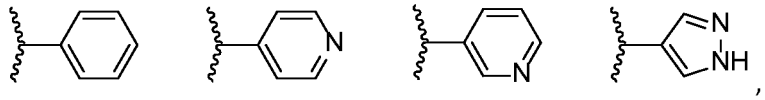
and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0116] In some embodiments according to Formula I or Formula Ia, R_3 is selected from, but not limited to, the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



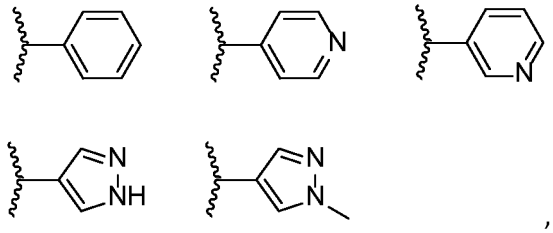
and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0117] In some embodiments according to Formula I or Formula Ia, R_3 is selected from, but not limited to, the following structures:



which may be optionally subsubstituted with alkyl (C_1-C_6); and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0118] In some embodiments according to Formula I or Formula Ia, R_3 is selected from, but not limited to, the following structures:



and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-156 herein.

[0119] In some embodiments according to Formula I or Formula Ia, R_3 is selected from phenyl groups which may be optionally substituted with 1 to 5 groups selected from R_5; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0120] In some embodiments according to Formula I or Formula Ia, R_3 is an unsubstituted phenyl group; and X, Y, Z, R_{1a}, R_{1b}, R_2, R_4, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0121] In some embodiment according to Formula I or Formula Ia, each R_4 is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, -SO_2Pr), and thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu); and X, Y, Z, R_{1a}, R_{1b}, R_2, R_3, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0122] In some embodiment according to Formula I or Formula Ia, each R_4 is independently selected from deuterium,

alkyl (C_1-C_3) (such as methyl, ethyl, propyl), alkoxy (C_1-C_3) (such as methoxy, ethoxy), and halogen (such as F, Cl); and X, Y, Z, R_{1a}, R_{1b}, R_2, R_3, and R_5 are as defined in any one or combination of paragraphs 83-124 herein.

[0123] In some embodiments according to Formula I or Formula Ia, each R_4 is independently selected from cycloalkyl (C_3-C_8) (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl); and X, Y, Z, R_{1a}, R_{1b}, R_2, R_3, and R_4 are as defined in any one or combination of paragraphs 83-124 herein.

[0124] In some embodiment according to Formula I or Formula Ia, each R_5 is independently selected from deuterium, alkyl (C_1-C_6) (such as methyl, ethyl, propyl, isopropyl, butyl), alkoxy (C_1-C_6) (such as methoxy, ethoxy, isopropoxy), amino (such as -NH_2, -NHMe, -NHEt, -NHiPr, -NHBu -NMe_2, NMeEt, -NEt_2, -NEtBu), -NHC(O)NH-alkyl(C_1-C_6), halogen (such as F, Cl), amide (such as -NHC(O)Me, -NHC(O)Et, - C(O)NHMe, -C(O)NEt_2, -C(O)NiPr), -CF_3, -CN, -N_3, ketone (such as acetyl, -C(O)Et, -C(O)Pr), -S(O)-alkyl(C_1-C_4) (such as -S(O)Me, -S(O)Et), -SO_2-alkyl(C_1-C_6) (such as -SO_2Me, -SO_2Et, -SO_2Pr), thioalkyl(C_1-C_6) (such as -SMe, -SEt, -SPr, -SBu), -COOH, and ester (such as -C(O)OMe, -C(O)OEt, -C(O)OBu); and X, Y, Z, R_{1a}, R_{1b}, R_2, R_3, and R_4 are as defined in any one or combination of paragraphs 83-123 herein.

[0125] In certain embodiments, the compound of Formula I or Formula Ia is selected from:

3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
Methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methylbenzoate;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methylbenzamide;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)benzamide;
4-Cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one;
3-(5-(5-acetylpyridin-3-yl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one formate;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-(Cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one;
4-(*tert*-Butyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one;
4-Cyclopentyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclohexyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(5-(1-Methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-4-neopentyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-ethyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(2-methoxyethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(3-methylbenzo[d]isoxazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(3-methyl-1*H*-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-3-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(2-(1*H*-Indol-6-yl)-5-(1-methyl-1*H*-indazol-6-yl)-1*H*-imidazol-4-yl)-4-cyclopropyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1*H*-pyrazol-4-yl)-1H-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4H)-one;

and stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof.

[0126] In certain embodiments, the compound of Formula I is 4-cyclopropyl-1-methyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0127] In certain embodiments, the pharmaceutically acceptable salt of a compound of Formula I is selected from a hydrochloride or dihydrochloride salt.

[0128] In certain embodiments, the pharmaceutically acceptable salt of a compound of Formula I or Formula Ia is

selected from:

3-(5-(3-acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methyl benzoate hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methyl benzamide hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl) benzamide hydrochloride;
4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(3-acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(3-acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(3-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride ;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride; and
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride; and

stereoisomers, tautomers, or hydrates thereof.

[0129] In certain embodiments, the pharmaceutically acceptable salt of a compound of Formula I is 4-cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride.

[0130] 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 or Formula Ia or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0131] In one embodiment, because of potent effects of BET inhibitors *in vitro* on IL-6 and IL-17 transcription, BET inhibitor compounds of Formula I or Formula Ia or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof may be used as therapeutics for inflammatory disorders in which IL-6 and/or IL-17 have been implicated in disease. The following autoimmune diseases are amenable to therapeutic use of BET inhibition by administration of a compound of Formula I or Formula Ia or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof because of a prominent role of IL-6 and/or IL-17: Acute Disseminated Encephalomyelitis (T. Ishizu et al., "CSF cytokine and chemokine profiles in acute disseminated encephalomyelitis," J Neuroimmunol 175(1-2): 52-8 (2006)), Agammaglobulinemia (M. Gonzalez-Serrano, et al.," Increased Pro-inflammatory Cytokine Production After Lipopolysaccharide Stimulation in Patients with X-linked Agammaglobulinemia," J Clin Immunol 32(5):967-74 (2012)), Allergic Disease (L. McKinley et al., "TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice," J Immunol 181(6):4089-97 (2008)), Ankylosing spondylitis (A. Taylan et al., "Evaluation of the T helper 17 axis in ankylosing spondylitis," Rheumatol Int 32(8):2511-5 (2012)), Anti-GBM/Anti-TBM nephritis (Y. Ito et al., "Pathogenic significance of interleukin-6 in a patient with antiglomerular basement membrane antibody-induced glomerulonephritis with multinucleated giant cells," Am J Kidney Dis 26(1):72-9 (1995)), Anti-phospholipid syndrome (P. Soltesz et al., "Immunological features of primary anti-phospholipid syndrome in connection with endothelial dysfunction," Rheumatology (Oxford) 47(11):1628-34 (2008)), Autoimmune aplastic anemia (Y. Gu et al., "Interleukin (IL)-17 promotes macrophages to produce IL-8, IL-6 and tumour necrosis factor-alpha in aplastic anaemia," Br J Haematol 142(1):109-14 (2008)), Autoimmune hepatitis (L. Zhao et al., "Interleukin-17 contributes to the pathogenesis of autoimmune hepatitis through inducing hepatic

interleukin-6 expression," PLoS One 6(4):e18909 (2011)), Autoimmune inner ear disease (B. Gloddek et al., "Pharmacological influence on inner ear endothelial cells in relation to the pathogenesis of sensorineural hearing loss," Adv Otorhinolaryngol 59:75-83 (2002)), Autoimmune myocarditis (T. Yamashita et al., "IL-6-mediated Th17 differentiation through RORgammat is essential for the initiation of experimental autoimmune myocarditis," Cardiovasc Res 91(4):640-8 (2011)), Autoimmune pancreatitis (J. Ni et al.," Involvement of Interleukin-17A in Pancreatic Damage in Rat Experimental Acute Necrotizing Pancreatitis," Inflammation (2012)), Autoimmune retinopathy (S. Hohki et al., "Blockade of interleukin-6 signaling suppresses experimental autoimmune uveoretinitis by the inhibition of inflammatory Th17 responses," Exp Eye Res 91(2):162-70 (2010)), Autoimmune thrombocytopenic purpura (D. Ma et al., "Profile of Th17 cytokines (IL-17, TGF-beta, IL-6) and Th1 cytokine (IFN-gamma) in patients with immune thrombocytopenic purpura," Ann Hematol 87(11):899-904 (2008)), Behcet's Disease (T. Yoshimura et al., "Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis," Rheumatology (Oxford) 48(4):347-54 (2009)), Bullous pemphigoid (L. D'Auria et al., "Cytokines and bullous pemphigoid," Eur Cytokine Netw 10(2):123-34 (1999)), Castleman's Disease (H. El-Osta and R. Kurzrock, "Castleman's disease: from basic mechanisms to molecular therapeutics," Oncologist 16(4):497-511 (2011)), Celiac Disease (A. Lahdenpera et al., "Up-regulation of small intestinal interleukin-17 immunity in untreated coeliac disease but not in potential coeliac disease or in type 1 diabetes," Clin Exp Immunol 167(2):226-34 (2012)), Churg-Strauss syndrome (A. 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Mok et al., "The relation of interleukin 17 (IL-17) and IL-23 to Th1/Th2 cytokines and disease activity in systemic lupus erythematosus," J Rheumatol 37(10):2046-52 (2010)), Microscopic polyangitis (A. Muller Kobold et al., "In vitro up-regulation of E-selectin and induction of interleukin-6 in endothelial cells by autoantibodies in Wegener's granulomatosis and microscopic polyangiitis," Clin Exp Rheumatol 17(4):433-40 (1999)), Multiple sclerosis (F. Jadidi-Niaragh and A. Mirshafiey, "Th17 cell, the new player of neuroinflammatory process in multiple sclerosis," Scand J Immunol 74(1):1-13

(2011)), Myasthenia gravis (R. Aricha et al., "Blocking of IL-6 suppresses experimental autoimmune myasthenia gravis," J Autoimmun 36(2):135-41 (2011)), myositis (G. Chevrel et al., "Interleukin-17 increases the effects of IL-1 beta on muscle cells: arguments for the role of T cells in the pathogenesis of myositis," J Neuroimmunol 137(1-2):125-33 (2003)), Optic neuritis (S. Icoz et al., "Enhanced IL-6 production in aquaporin-4 antibody positive neuromyelitis optica patients," Int J Neurosci 120(1):71-5 (2010)), Pemphigus (E. Lopez-Robles et al., "TNFalpha and IL-6 are mediators in the blistering process of pemphigus," IntJ Dermatol 40(3):185-8 (2001)), POEMS syndrome (K. Kallen et al., "New developments in IL-6 dependent biology and therapy: where do we stand and what are the options?" Expert Opin Investig Drugs 8(9):1327-49 (1999)), Polyarteritis nodosa (T. Kawakami et al., "Serum levels of interleukin-6 in patients with cutaneous polyarteritis nodosa," Acta Derm Venereol 92(3):322-3 (2012)), Primary biliary cirrhosis (K. Harada et al., "Periductal interleukin-17 production in association with biliary innate immunity contributes to the pathogenesis of cholangiopathy in primary biliary cirrhosis," Clin Exp Immunol 157(2):261-70 (2009)), Psoriasis (S. Fujishima et al., "Involvement of IL-17F via the induction of IL-6 in psoriasis," Arch Dermatol Res 302(7):499-505 (2010)), Psoriatic arthritis (S. Raychaudhuri et al., IL-17 receptor and its functional significance in psoriatic arthritis," Mol Cell Biochem 359(1-2):419-29 (2012)), Pyoderma gangrenosum (T. Kawakami et al., "Reduction of interleukin-6, interleukin-8, and anti-phosphatidylserine-prothrombin complex antibody by granulocyte and monocyte adsorption apheresis in a patient with pyoderma gangrenosum and ulcerative colitis," Am J Gastroenterol 104(9):2363-4 (2009)), Relapsing polychondritis (M. Kawai et al., "Sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in two patients with refractory relapsing polychondritis," Rheumatology (Oxford) 48(3):318-9 (2009)), Rheumatoid arthritis (Z. Ash and P. Emery, "The role of tocilizumab in the management of rheumatoid arthritis," Expert Opin Biol Ther, 12(9):1277-89 (2012)), Sarcoidosis (F. Belli et al., "Cytokines assay in peripheral blood and bronchoalveolar lavage in the diagnosis and staging of pulmonary granulomatous diseases," Int J Immunopathol Pharmacol 13(2):61-67 (2000)), Scleroderma (T. Radstake et al., "The pronounced Th17 profile in systemic sclerosis (SSc) together with intracellular expression of TGFbeta and IFNgamma distinguishes SSc phenotypes," PLoS One, 4(6): e5903 (2009)), Sjogren's syndrome (G. Katsifis et al., "Systemic and local interleukin-17 and linked cytokines associated with Sjogren's syndrome immunopathogenesis," Am J Pathol 175(3):1167-77 (2009)), Takayasu's arteritis (Y. Sun et al., "MMP-9 and IL-6 are potential biomarkers for disease activity in Takayasu's arteritis," Int J Cardiol 156(2):236-8 (2012)), Transverse myelitis (J. Graber et al., "Interleukin-17 in transverse myelitis and multiple sclerosis," J Neuroimmunol 196(1-2):124-32 (2008)), Ulcerative colitis (J. Mudter and M. Neurath, "Il-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance," Inflamm Bowel Dis 13(8):1016-23 (2007)), Uveitis (H. Haruta et al., "Blockade of interleukin-6 signaling suppresses not only th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis," Invest Ophthalmol Vis Sci 52(6):3264-71 (2011)), and Vitiligo (D. Bassiouny and O. 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 or Formula Ia, 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.

[0132] Acute and chronic (non-autoimmune) inflammatory diseases characterized by increased expression of pro-inflammatory cytokines, including IL-6, MCP-1, and IL-17, would also be amenable to therapeutic BET inhibition. These include, but are not limited to, sinusitis (D. Bradley and S. Kountakis, "Role of interleukins and transforming growth factor-beta in chronic rhinosinusitis and nasal polyposis," Laryngoscope 115(4):684-6 (2005)), pneumonitis (Besnard, A.G., et al., "Inflammasome-IL-1-Th17 response in allergic lung inflammation" J Mol Cell Biol 4(1):3-10 (2012)), osteomyelitis (T. Yoshii et al., "Local levels of interleukin-lbeta, -4, -6 and tumor necrosis factor alpha in an experimental model of murine osteomyelitis due to staphylococcus aureus," Cytokine 19(2):59-65 2002), gastritis (T. Bayraktaroglu et al., "Serum levels of tumor necrosis factor-alpha, interleukin-6 and interleukin-8 are not increased in dyspeptic patients with Helicobacter pylori-associated gastritis," Mediators Inflamm 13(1):25-8 (2004)), enteritis (K. Mitsuyama et al., "STAT3 activation via interleukin 6 trans-signalling contributes to ileitis in SAMP1/Yit mice," Gut 55(9):1263-9. (2006)), gingivitis (R. Johnson et al., "Interleukin-11 and IL-17 and the pathogenesis of periodontal disease," J Periodontol 75(1):37-43 (2004)), appendicitis (S. Latifi et al., "Persistent elevation of serum interleukin-6 in intraabdominal sepsis identifies those with prolonged length of stay," J Pediatr Surg 39(10):1548-52 (2004)), irritable bowel syndrome (M. Ortiz-Lucas et al., "Irritable bowel syndrome immune hypothesis. Part two: the role of cytokines," Rev Esp Enferm Dig 102(12):711-7 (2010)), tissue graft rejection (L. Kappel et al., "IL-17 contributes to CD4-mediated graft-versus-host disease," Blood 113(4):945-52 (2009)), chronic obstructive pulmonary disease (COPD) (S. Traves and L. Donnelly, "Th17 cells in airway diseases," Curr Mol Med 8(5):416-26 (2008)), septic shock (toxic shock syndrome, SIRS, bacterial sepsis, etc) (E. Nicodeme et al., Nature 468(7327):1119-23 (2010)), osteoarthritis (L. Chen et al., "IL-17RA aptamer-mediated repression of IL-6 inhibits synovium inflammation in a murine model of osteoarthritis," Osteoarthritis Cartilage 19(6):711-8 (2011)), acute gout (W. Urano et al., "The inflammatory process in the mechanism of decreased serum uric acid concentrations during acute gouty arthritis," J Rheumatol 29(9):1950-3 (2002)), acute lung injury (S. Traves and L. Donnelly, "Th17 cells in airway diseases," Curr Mol Med 8(5):416-26 (2008)), acute renal failure (E. Simmons et al., "Plasma cytokine levels predict mortality in patients with acute renal failure," Kidney Int 65(4):1357-65 (2004)), burns (P. Paquet and G.

Pierard, "Interleukin-6 and the skin," Int Arch Allergy Immunol 109(4):308-17 (1996)), Herxheimer reaction (G. Kaplanski et al., "Jarisch-Herxheimer reaction complicating the treatment of chronic Q fever endocarditis: elevated TNFalpha and IL-6 serum levels," J Infect 37(1):83-4 (1998)), and SIRS associated with viral infections (A. Belkinaand G. Denis, Nat Rev Cancer 12(7):465-77 (2012)). Thus, the invention includes compounds of Formula I or Formula Ia, 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.

[0133] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, 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 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 (A. Kimura and T. Kishimoto, "IL-6: regulator of Treg/Th17 balance," Eur J Immunol 40(7):1830-5 (2010)) and thus would be especially sensitive to BET inhibition. In another embodiment, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof may be used for treating sepsis and associated afflictions. BET inhibition has been shown to inhibit development of sepsis, in part, by inhibiting IL-6 expression, in preclinical models in both published (E. Nicodeme et al., Nature 468(7327):1119-23 (2010)) and proprietary data.

[0134] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, 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 myc family oncoproteins (MYCN, L-myc) are particularly sensitive to BET inhibition. J. Delmore et al., Cell 146(6):904-17 (2010); J. Mertz et al., 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, 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. M. Vita and M. Henriksson, Semin Cancer Biol 16(4):318-30 (2006).

[0135] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat cancers that result from an aberrant regulation (overexpression, translocation, etc) of BET proteins. These include, but are not limited to, NUT midline carcinoma (Brd3 or Brd4 translocation to nutlin 1 gene) (C. French Cancer Genet Cytogenet 203(1):16-20 (2010)), β-cell lymphoma (Brd2 overexpression) (R. Greenwald et al., Blood 103(4):1475-84 (2004)), non-small cell lung cancer (BrdT overexpression) (C. Grunwald et al., "Expression of multiple epigenetically regulated cancer/germline genes in nonsmall cell lung cancer," Int J Cancer 118(10):2522-8 (2006)), esophageal cancer and head and neck squamous cell carcinoma (BrdT overexpression) (M. Scanlan et al., "Expression of cancer-testis antigens in lung cancer: definition of bromodomain testis-specific gene (BRDT) as a new CT gene, CT9," Cancer Lett 150(2):55-64 (2000)), and colon cancer (Brd4) (R. Rodriguez et al., "Aberrant epigenetic regulation of bromodomain BRD4 in human colon cancer," J Mol Med (Berl) 90(5):587-95 (2012)).

[0136] In one embodiment, because BET inhibitors decrease Brd-dependent recruitment of pTEFb to genes involved in cell proliferation, BET inhibitor compounds of Formula I or Formula Ia, 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 (W. Tong 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 (C. Bellan et al., "CDK9/CYCLIN T1 expression during normal lymphoid differentiation and malignant transformation," J Pathol 203(4):946-52 (2004)), neuroblastoma and primary neuroectodermal tumor (G. De Falco et al., "Cdk9 regulates neural differentiation and its expression correlates with the differentiation grade of neuroblastoma and PNET tumors," Cancer Biol Ther 4(3):277-81 (2005)), rhabdomyosarcoma (C. Simone and A. Giordano, "Abrogation of signal-dependent activation of the cdk9/cyclin T2a complex in human RD rhabdomyosarcoma cells," Cell Death Differ 14(1):192-5 (2007)), prostate cancer (D. Lee et al., "Androgen receptor interacts with the positive elongation factor P-TEFb and enhances the efficiency of transcriptional elongation," J Biol Chem 276(13):9978-84 (2001)), and breast cancer (K. Bartholomeeusen et al., "BET bromodomain inhibition activates transcription via a transient release of P-TEFb from 7SK snRNP," J Biol Chem (2012)).

[0137] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be

used to treat cancers in which BET-responsive genes, such as CDK6, Bcl2, TYRO3, MYB, and hTERT are up-regulated. M. Dawson et al., Nature 478(7370):529-33 (2011); J. Delmore et al., Cell 146(6):904-17 (2010). These cancers include, but are not limited to, 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 β-cell lymphoma, small cell lung cancer, and renal carcinoma. M. Ruden and N. Puri, "Novel anticancer therapeutics targeting telomerase," Cancer Treat Rev (2012); P. Kelly and A. Strasser, "The role of Bcl-2 and its pro-survival relatives in tumourigenesis and cancer therapy" Cell Death Differ 18(9):1414-24 (2011); T. Uchida et al., "Antitumor effect of bcl-2 antisense phosphorothioate oligodeoxynucleotides on human renal-cell carcinoma cells in vitro and in mice," Mol Urol 5(2):71-8 (2001).

[0138] 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 or Formula Ia, 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 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 (PML), and non-Hodgkin's lymphoma. P. Filippakopoulos et al., Nature 468(7327):1067-73 (2010); M. Dawson et al., Nature 478(7370):529-33 (2011); Zuber, J., et al., "RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia," Nature 478(7370):524-8 (2011); M. Segura,et al, Cancer Research. 72(8):Supplement 1 (2012). The compounds of the invention have a demonstrated BET inhibition effect on cell proliferation *in vitro* for the following cancers: Neuroblastoma, Medulloblastoma, lung carcinoma (NSCLC, SCLC), and colon carcinoma.

[0139] In one embodiment, because of potential synergy or additive effects between BET inhibitors and other cancer therapy, BET inhibitor compounds of Formula I or Formula Ia, 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 antiproliferative 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 (Velcade), Busulfan (Myleran), Camptothecin, Cisplatin, Cyclophosphamide (Clafen), CYT387, Cytarabine (Ara-C), Dacarbazine, DAPT (GSI-IX), Decitabine, Dexamethasone, Doxorubicin (Adriamycin), Etoposide, Everolimus (RAD001), Flavopiridol (Alvocidib), Ganetespib (STA-9090), Gefitinib (Iressa), Idarubicin, Ifosfamide (Mitoxana), IFNa2a (Roferon A), Melphalan (Alkeran), Methazolastone (temozolomide), Metformin, Mitoxantrone (Novantrone), Paclitaxel, Phenformin, PKC412 (Midostaurin), PLX4032 (Vemurafenib), Pomalidomide (CC-4047), Prednisone (Deltasone), Rapamycin, Revlimid (Lenalidomide), Ruxolitinib (INCB018424), Sorafenib (Nexavar), SU11248 (Sunitinib), SU11274, Vinblastine, Vincristine (Oncovin), Vinorelbine (Navelbine), Vorinostat (SAHA), and WP1130 (Degrasyn).

[0140] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, 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, 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. X. Tanget al., Am J Pathology in press (2013).

[0141] In one embodiment, because of their ability to up-regulate ApoA-1 transcription and protein expression (O. Mirguet et al., Bioorg Med Chem Lett 22(8):2963-7 (2012); C. Chung et al., J Med Chem 54(11):3827-38 (2011)), BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used to treat cardiovascular diseases that are generally associated with including dyslipidemia, atherosclerosis, hypercholesterolemia, and metabolic syndrome (A. Belkina and G. Denis, Nat Rev Cancer 12(7):465-77 (2012); G. Denis Discov Med 10(55):489-99 (2010)). In another embodiment, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, may be used to treat non-cardiovascular disease characterized by deficits in ApoA-1, including Alzheimer's disease. D. Elliott et al., Clin Lipidol 51(4):555-573 (2010).

[0142] In one embodiment, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used in patients with insulin resistance and type II diabetes. A. Belkina and G. Denis, Nat Rev Cancer 12(7):465-77 (2012); G. Denis Discov Med 10(55):489-99 (2010); F. Wang et al., Biochem J 425(1):71-83 (2010); G. Denis et al,

FEBS Lett 584(15):3260-8 (2010). The anti-inflammatory effects of BET inhibition would have additional value in decreasing inflammation associated with diabetes and metabolic disease. K. Alexandraki et al., "Inflammatory process in type 2 diabetes: The role of cytokines," Ann N Y Acad Sci 1084:89-117 (2006).

[0143] In one embodiment, because of their ability to down-regulate viral promoters, BET inhibitor compounds of Formula I or Formula Ia, 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), Merkel cell polyomavirus, and human cytomegalovirus (CMV). D. Gagnon et al., J Virol 83(9):4127-39 (2009); J. You et al., J Virol 80(18):8909-19 (2006); R. Palermo et al., "RNA polymerase II stalling promotes nucleosome occlusion and pTEFb recruitment to drive immortalization by Epstein-Barr virus," PLoS Pathog 7(10):e1002334 (2011); E. Poreba et al., "Epigenetic mechanisms in virus-induced tumorigenesis," Clin Epigenetics 2(2):233-47. 2011. In another embodiment, because of their ability to reactivate HIV-1 in models of latent T cell infection and latent monocyte infection, BET inhibitors could be used in combination with anti-retroviral therapeutics for treating HIV. J. Zhu, et al., Cell Rep (2012); C. Banerjee et al., J Leukoc Biol (2012); K. Bartholomeeusen et al., J Biol Chem (2012); Z. Li et al., Nucleic Acids Res (2012.)

[0144] In one embodiment, because of the role of epigenetic processes and bromodomain-containing proteins in neurological disorders, BET inhibitor compounds of Formula I or Formula Ia, 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. R. Prinjha et al., Trends Pharmacol Sci 33(3):146-53 (2012); S. Muller et al., "Bromodomains as therapeutic targets," Expert Rev Mol Med 13:e29 (2011).

[0145] In one embodiment, because of the effect of BRDT depletion or inhibition on spermatid development, BET inhibitor compounds of Formula I or Formula Ia, stereoisomers, tautomers, pharmaceutically acceptable salts, or hydrates thereof, or compositions comprising one or more of those compounds may be used as reversible, male contraceptive agents. M. Matzuk et al., "Small-Molecule Inhibition of BRDT for Male Contraception," Cell 150(4): p. 673-684 (2012); B. Berkovits et al., "The testis-specific double bromodomain-containing protein BRDT forms a complex with multiple spliceosome components and is required for mRNA splicing and 3'-UTR truncation in round spermatids," Nucleic Acids Res 40(15):7162-75 (2012).

Pharmaceutical Compositions

[0146] Pharmaceutical compositions of the present disclosure comprise at least one compound of Formula I or Formula Ia, 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] Formulations of the present disclosure suitable for parenteral administration comprise sterile aqueous preparations of at least one compound of Formula I or Formula Ia or tautomer, stereoisomer, pharmaceutically acceptable salt, or hydrate 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.

[0151] 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.

[0152] 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, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound (i.e., at least one compound of Formula I or Formula Ia or tautomer, stereoisomer, pharmaceutically acceptable salt, or hydrate 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%.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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 Table 1 for Equivalent Surface Area Dosage Factors).

Table 1. Equivalent Surface Area Dosage Factors:

To: / From:	Mouse (20 g)	Rat (150 g)	Monkey (3.5 kg)	Dog (8 kg)	Human (60 kg)
Mouse	1	1/2	1/4	1/6	1/12
Rat	2	1	1/2	1/4	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	3/5	1	1/2
Human	12	7	3	2	1

[0157] 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 severity 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.

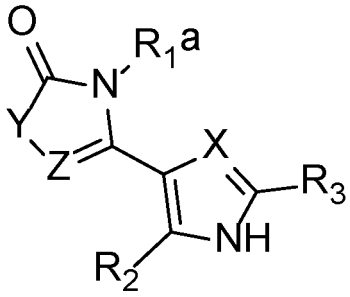
[0158] In one embodiment, a compound of Formula I or Formula Ia or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof, is administered in combination with another therapeutic agent. The other therapeutic agent can provide additive or synergistic value relative to the administration 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 cholesteryl 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-lowing drug; an HDL-raising drug; an HDL enhancer; a regulator of the apolipoprotein A-IV and/or apolipoprotein genes; or any cardiovascular drug.

[0159] In another embodiment, a compound of Formula I or Formula Ia 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; methylprenisolone (Medrol®), triamcinolone, methotrexate (Rheumatrex®, Trexall®), hydroxychloroquine (Plaquenil®), sulfasalzine (Azulfidine®), leflunomide (Arava®), etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), rituximab (Rituxan®), abatacept (Orencia®), interleukin-1, anakinra (Kineret™), ibuprofen, ketoprofen, fenoprofen, naproxen, aspirin, acetominophen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine, or sulfasalazine.

List of Exemplary Embodiments

[0160]

1. A compound of Formula I:

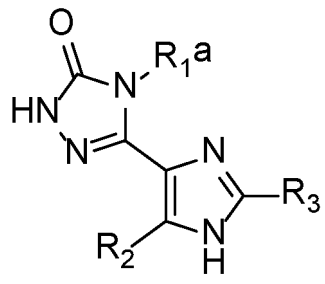


Formula I

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

X is selected from CH and N;
Y is selected from -NH, -N-R_{1b} and oxygen;
Z is selected from N, and -CH-;
$\mathbf{R_{1a}}$ and $\mathbf{R_{1b}}$ are independently selected from alkyl (C_1-C_6), carbocycle (C_3-C_{10}), heterocycle (C_2-C_{10}) optionally substituted with 1 to 3 groups selected from R_4;
$\mathbf{R_2}$ is selected from aryl (C_5-C_{10}) and heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
$\mathbf{R_3}$ is selected from carbocycle (C_3-C_{10}) and heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6), cycloalkyl (C_3-C_8), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thio-alkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and
each $\mathbf{R_5}$ is independently selected from deuterium, alkyl (C_1-C_6), alkoxy(C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_ralkyl(C_1-C_6), thioalkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

2. A compound according to embodiment 1, wherein the compound is a compound of Formula Ia:



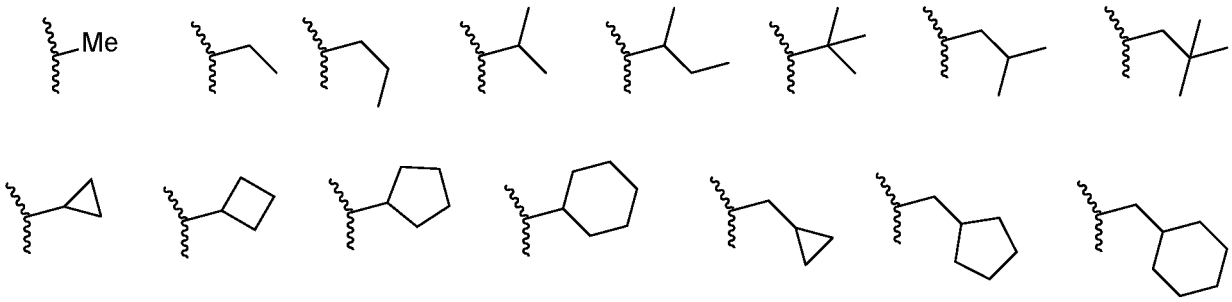
Formula Ia

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

$\mathbf{R_{1a}}$ is selected from alkyl (C_1-C_6), carbocycle (C_3-C_{10}), heterocycle (C_2-C_{10}) optionally substituted with 1 to 3 groups selected from R_4;
$\mathbf{R_2}$ is selected from aryl (C_5-C_{10}) and heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
$\mathbf{R_3}$ is selected from carbocycle (C_3-C_{10}) and heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5;
each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6), cycloalkyl (C_3-C_8), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thio-alkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and

each **R_5** is independently selected from deuterium, alkyl (C_1-C_6), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone (C_1-C_6), -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thio-alkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

3. The compound according to embodiment 1, wherein X is N.
4. The compound according to embodiment 1, wherein X is CH.
5. The compound according to embodiment 1, wherein Y is -NR_{1b}.
6. The compound according to embodiment 1, wherein Y is -NH.
7. The compound according to embodiment 1, wherein Y is oxygen.
8. The compound according to embodiment 1, wherein Z is N.
9. The compound according to embodiment 1, wherein Z is CH.
10. The compound according to embodiment 1 or embodiment 2, wherein each **R_4** is independently selected from deuterium, alkyl (C_1-C_6), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thioalkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.
11. The compound according to any one of embodiments 1-10, wherein R_{1a} is selected from alkyl (C_1-C_6), carbocycle (C_3-C_6), and heterocycle (C_2-C_5) optionally substituted with 1 to 3 groups selected from R_4.
12. The compound according to any one of embodiments 1-11, wherein R_{1a} is selected from alkyl (C_1-C_6) and carbocycle (C_3-C_6) optionally substituted with 1 to 3 groups selected from R_4.
13. The compound according to any one of embodiments 1-12, wherein R_{1a} is selected from the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:



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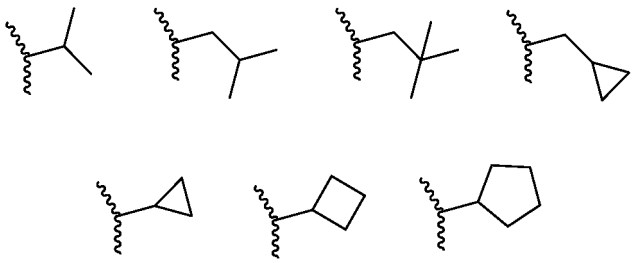
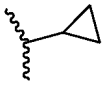
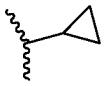
14. The compound according to any one of embodiments 1-13, wherein R_{1a} is selected from the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:



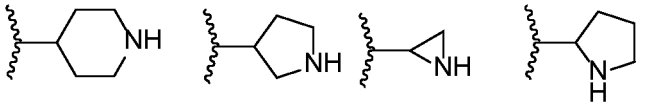
15. The compound according to any one of embodiments 1-14, wherein R_{1a} is



optionally substituted with with 1 to 3 groups selected from R_4.
16. The compound according to any one of embodiments 1-15, wherein R_{1a} is



17. The compound according to any one of embodiments 1-11, wherein R_{1a} is selected from the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:



18. The compound according to any one of embodiments 1, 3-5, and 7-17, wherein R_{1b} is alkyl (C_1-C_6).

19. The compound according to any one of embodiments 1, 3-5, and 7-18, wherein R_{1b} is selected from methyl and ethyl.

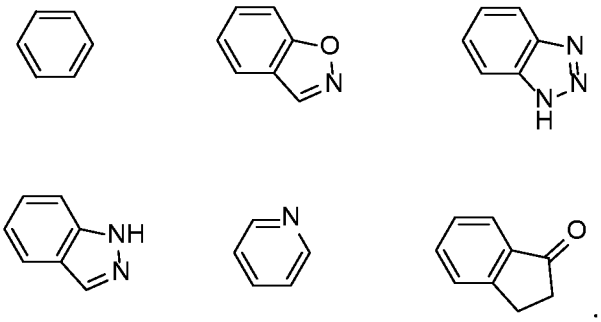
20. The compound according to any one of embodiments 1, 3-5, and 7-19, wherein R_{1b} is methyl.

21. The compound according to any one of embodiments 1-20, wherein R_2 is selected from bicyclic aryl and bicyclic heteroaryl groups optionally substituted with 1 to 5 R_5 groups.

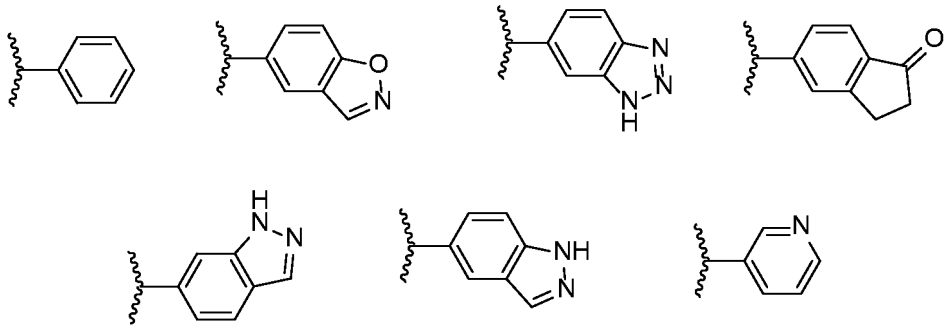
22. The compound according to any one of embodiments 1-21, wherein R_2 is selected from aryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5.

23. The compound according to any one of embodiments 1-21, wherein R_2 is selected from heteroaryl (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5.

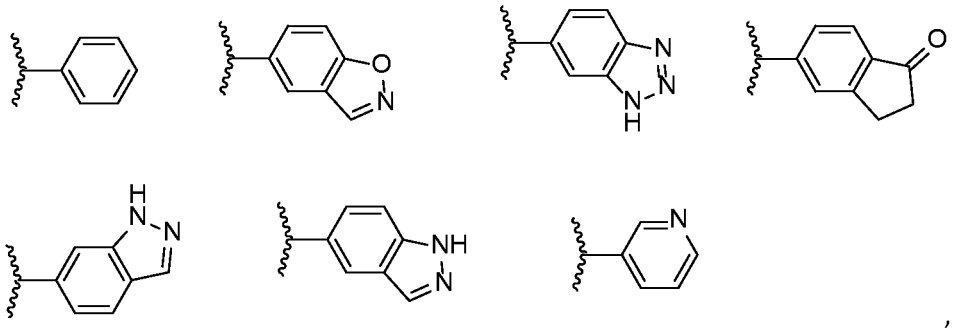
24. The compound according to any one of embodiments 1-23, wherein R_2 is selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



25. The compound according to any one of embodiments 1-24, wherein R_2 is selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:

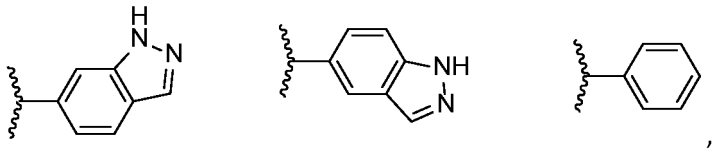


26. The compound according to any one of embodiments 1-25, wherein R_2 is selected from the following:



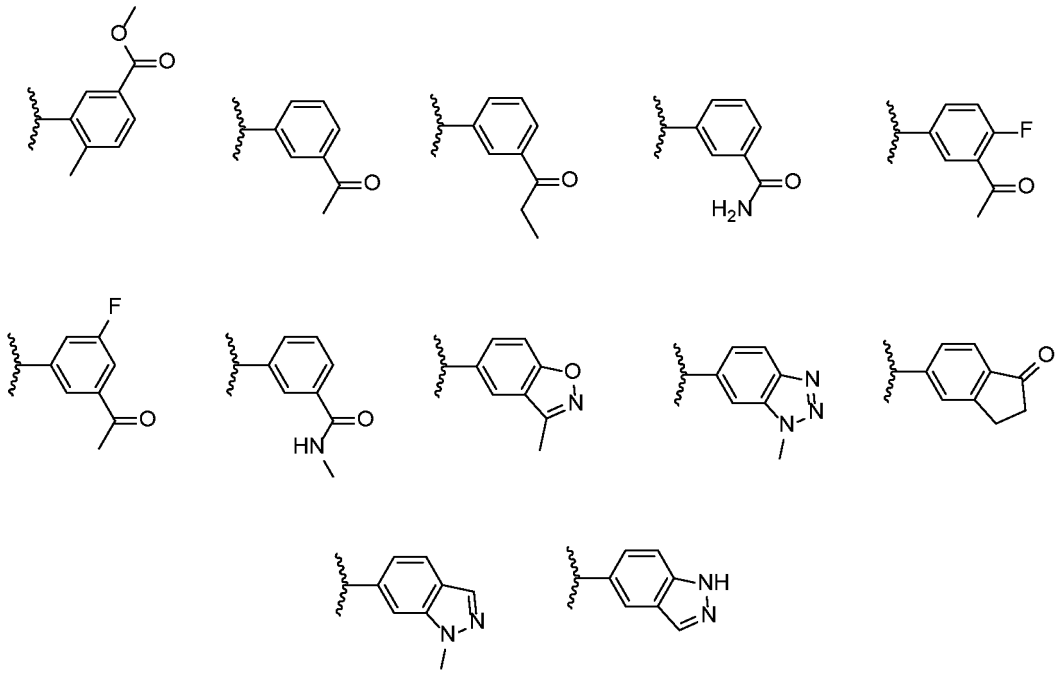
which may be optionally substituted with 1 to 2 groups selected from alkyl (C_1-C_6), halogen, ketone, amide, and ester.

27. The compound according to any one of embodiments 1-26, wherein R_2 is selected from the following:

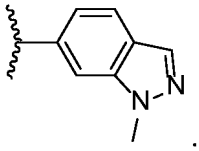


which may be optionally substituted with 1 to 2 groups selected from alkyl (C_1-C_6), halogen, ketone, amide, and ester.

28. The compound according to any one of embodiments 1-27, wherein R_2 is selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



29. The compound according to any one of embodiments 1-21 or 23-28, wherein R_2 is

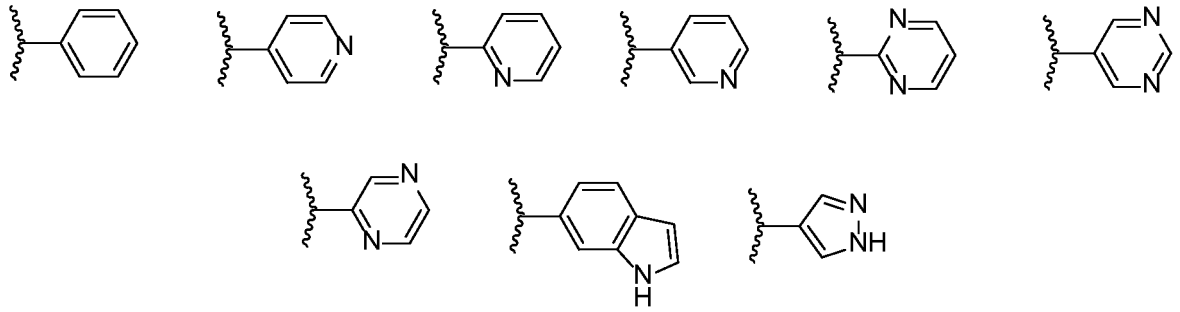


30. The compound according to any one of embodiments 1-29, wherein R_3 is selected from carbocycle (C_3-C_{10}) optionally substituted with 1 to 5 groups selected from R_5.

31. The compound according to any one of embodiments 1-30, wherein R_3 is selected from aryl groups (C_5-C_{10}) optionally substituted with 1 to 5 groups selected from R_5.

32. The compound according to any one of embodiments 1-29, wherein R_3 is selected from heterocycle (C_2-C_{10}) optionally substituted with 1 to 5 groups selected from R_5.

33. The compound according to any one of embodiments 1-32, wherein R_3 is selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



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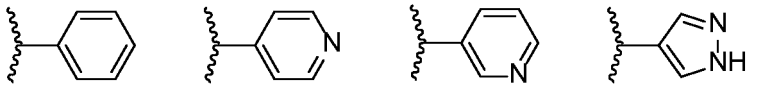
34. The compound according to any one of embodiments 1-33, wherein R_3 is selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



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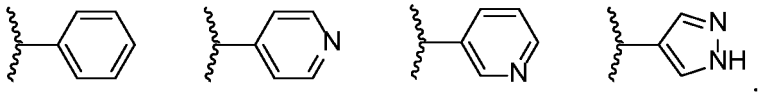
35. The compound according to any one of embodiments 1-34, wherein R_3 is selected from the following structures, which may be optionally substituted with alkyl (C_1-C_6):



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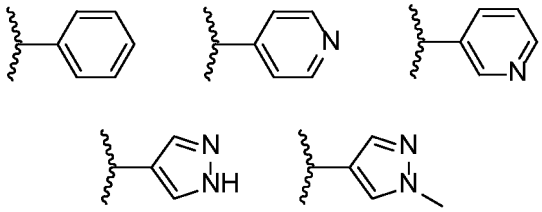
36. The compound according to any one of embodiments 1-35, wherein R_3 is selected from the following structures:



37. The compound according to any one of embodiments 1-36, wherein R_3 is selected from phenyl groups which may be optionally substituted with 1 to 5 groups selected from R_5.

38. The compound according to any one of embodiments 1-37, wherein R_3 is an unsubstituted phenyl group.

39. The compound according to any one of embodiments 1-38, wherein each R_4 is independently selected from deuterium, alkyl (C_1-C_6), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), and thioalkyl(C_1-C_6).

40. The compound according to any one of embodiments 1-39, wherein each R_4 is independently selected from deuterium, alkyl (C_1-C_3), alkoxy (C_1-C_3), and halogen.

41. The compound according to any one of embodiments 1-40, wherein each R_5 is independently selected from deuterium, alkyl (C_1-C_6), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thioalkyl(C_1-C_6), -COOH, and ester.

42. The compound according to embodiment 1 or embodiment 2, wherein the compound of Formula I or Formula

Ia is selected from:

3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
Methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methylbenzoate;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methylbenzamide;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)benzamide;
4-Cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
3-(5-(5-acetylpyridin-3-yl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one formate;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-(Cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-(*tert*-Butyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4H)-one;
4-Cyclopentyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclohexyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(5-(1-Methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-4-neopentyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-methyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-ethyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(2-methoxyethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(3-methylbenzo[d]isoxazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(5-(3-methyl-1*H*-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(2-(1*H*-Indol-6-yl)-5-(1-methyl-1*H*-indazol-6-yl)-1*H*-imidazol-4-yl)-4-cyclopropyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;

and stereoisomers, tautomers, pharmaceutically acceptable salts, and hydrates thereof.

43. The compound of embodiment 1 or embodiment 2, wherein the compound of Formula I or Formula Ia is selected from the following:

3-(5-(3-acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methyl benzoate hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methyl benzamide hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl) benzamide hydrochloride;
4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydro-

chloride;
3-(5-(3-acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(3-acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(3-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride; and

and stereoisomers, tautomers, and hydrates thereof.

44. A pharmaceutical composition comprising the compound of any one of embodiments 1-43, and a pharmaceutically acceptable carrier.

45. method for inhibition of BET protein function comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

46. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

47. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

48. A method of treating a cancer associated with overexpression, translocation, amplification, or rearrangement of a myc family oncoprotein that is sensitive to BET inhibition comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

49. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

50. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

51. A method of treating a cancer associated with upregulation of BET responsive genes CDK6, Bcl2, TYRO3, MYB, and hTERT comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

52. A method of treating a cancer associated with a gene regulated by a super enhancer comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

53. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

54. A method of treating a cancer that is resistant to treatment with immunotherapy, hormone-deprivation therapy, and/or chemotherapy comprising administering a therapeutically effective amount of the compound of any one of

embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

55. The method of any one of embodiments 45-54, wherein the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44 is combined with other therapies, chemotherapeutic agents or antiproliferative agents.

56. The method of embodiment 55, wherein the therapeutic agent is selected from ABT-737, Azacitidine (Vidaza), AZD1152 (Barasertib), AZD2281 (Olaparib), AZD6244 (Selumetinib), BEZ235, Bleomycin Sulfate, Bortezomib (Velcade), Busulfan (Myleran), Camptothecin, Cisplatin, Cyclophosphamide (Clafen), CYT387, Cytarabine (Ara-C), Dacarbazine, DAPT (GSI-IX), Decitabine, Dexamethasone, Doxorubicin (Adriamycin), Etoposide, Everolimus (RAD001), Flavopiridol (Alvocidib), Ganetespib (STA-9090), Gefitinib (Iressa), Idarubicin, Ifosfamide (Mitoxana), IFNa2a (Roferon A), Melphalan (Alkeran), Methazolastone (temozolomide), Metformin, Mitoxantrone (Novantrone), Paclitaxel, Phenformin, PKC412 (Midostaurin), PLX4032 (Vemurafenib), Pomalidomide (CC-4047), Prednisone (Deltasone), Rapamycin, Revlimid (Lenalidomide), Ruxolitinib (INCB018424), Sorafenib (Nexavar), SU11248 (Sunitinib), SU11274, Vinblastine, Vincristine (Oncovin), Vinorelbine (Navelbine), Vorinostat (SAHA), and WP1130 (Degrasyn).

57. 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, 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 comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

58. A method of treating a disease or disorder that benefits from up-regulation or ApoAI transcription and protein expression comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

59. A method of treating a metabolic disease or disorder comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

60. A method of treating a cancer associated with a virus comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

61. A method for treating HIV infection comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44 alone or in combination with anti-retroviral therapeutic.

62. 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 embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

63. A method of male contraception comprising administering a therapeutically effective amount of the compound of any one of embodiments 1-43 or a pharmaceutical composition according to embodiment 44.

64. The method of embodiment 46, wherein the autoimmune or inflammatory disorder is selected from Acute Disseminated Encephalomyelitis, Agammaglobulinemia, Allergic Disease, Ankylosing spondylitis, Anti-GBM/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, Eosinophlic 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, idiopathic pulmonary fibrosis, IgA nephropathy, Inclusion body myositis, Type I diabetes, Interstitial cystitis, Kawasaki's Disease, Leukocytoclastic vasculitis, Lichen planus, Lupus (SLE), Microscopic polyangitis, 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.

65. The method of embodiment 47, 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.

66. The method of embodiment 47, wherein the acute or chronic non-autoimmune inflammatory disorder is selected from rheumatoid arthritis (RA) and multiple sclerosis (MS).

67. The method of embodiment 48, 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.

68. The method of embodiment 49, wherein the cancer is selected from NUT midline carcinoma, β-cell lymphoma, non-small cell lung cancer, esophageal cancer, head and neck squamous cell carcinoma, breast cancer, prostate cancer, and colon cancer.

69. The method of embodiment 50, 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.

70. The method of embodiment 51, 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 β-cell lymphoma, small cell lung cancer, and renal carcinoma.

71. The method of embodiment 52, wherein the gene is the MYC oncogene.

72. The method of embodiment 53, 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), breast cancer, prostate cancer, and colon carcinoma.

73. The method of embodiment 53, wherein the cancer is selected from adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute myeloid leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, β-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large β-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, Leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone β-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, Merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mixed lineage leukemia, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, NUT-midline carcinoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, primary peritoneal cancer,

prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

74. The method of embodiment 58, wherein the disease is cardiovascular disease, dyslipidemia, atheroschlerosis, hypercholesterolemia, metabolic syndeome, and Alzheimer's disease.

75. The method of embodiment 59, wherein the metabolic disorder is selected from obesity-associated inflammation, type II diabetes, and insulin resistance.

76. The method of embodiment 60, 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).

Examples

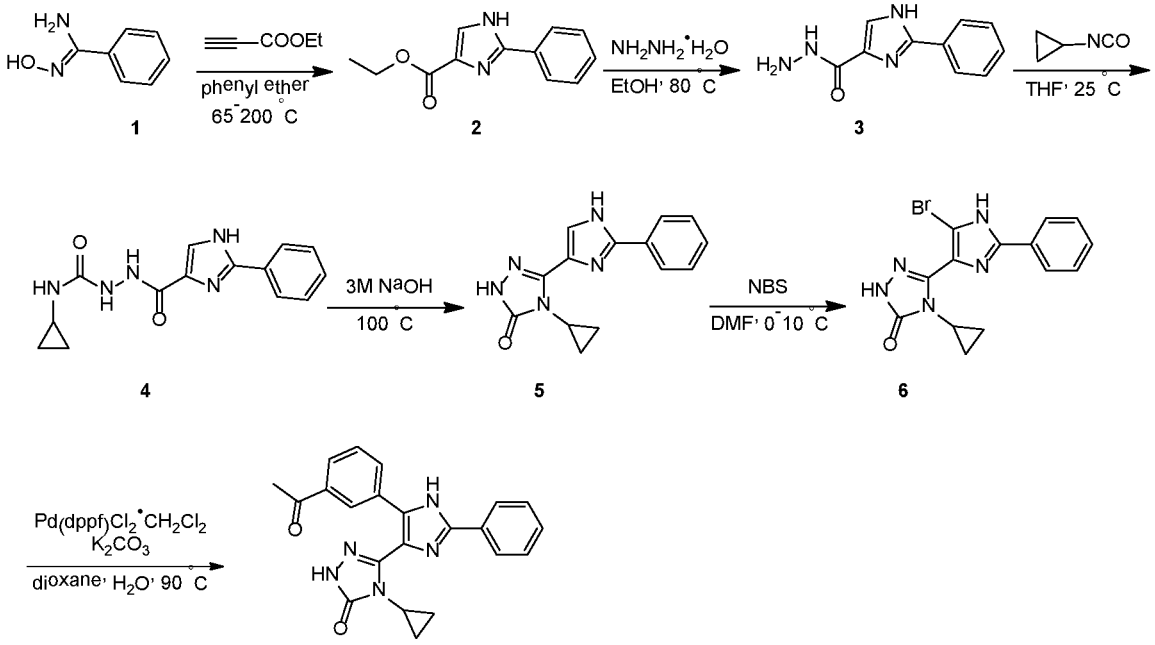
[0161] General Methods. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker 400 MHz spectrometer. Spectra are given in ppm (δ) and coupling constants, J values, are reported in hertz (Hz). Mass spectra analyses were performed on Shimadzu 2020 Mass Spectrometer in ESI or APCI mode when appropriate.

[0162] Abbreviations: DCM: dichloromethane; DMF: dimethylformamide; EtOAc: ethyl acetate; NBS: *N*-bromosuccinimide; MeOH: methanol; PE: petroleum ether; SEM-Cl: (2-(chloromethoxy)ethyl)trimethylsilane;TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography.

General Procedure A:

Example 1: Preparation of 3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one

[0163]



Example 1

[0164] A solution of compound 1 (25.0 g, 184 mmol, 1.00 *eq*), ethyl prop-2-ynoate (18.0 g, 184 mmol, 1.0 *eq)* in MeOH (200 mL) was heated at 65 °C for 16 h. After cooling to 25 °C, MeOH was removed under reduced pressure and the residue was purified by column chromatography (PE: EtOAc = 3:1) to give an oil. The oil was dissolved in phenyl ether (200 mL) and heated at 200 °C for 30 min. TLC indicated conversion to a new spot. The reaction mixture was cooled to 25 °C and poured into petroleum ether (500 mL), extracted with 1N HCl (2 x 200 mL). The combined aqueous layers were carefully diluted with sodium bicarbonate to basic pH and extracted with ethyl acetate (5 x 200 mL). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (3:1 PE:EtOAc) and washed with DCM (200 mL) to afford **2** (18.0 g, 83.2 mmol, 45 % yield) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.03 Hz, 3H), 4.26 (q, *J*=6.94 Hz, 2H), 7.36 - 7.54 (m, 3H), 7.92 - 8.02 (m, 2H), 8.13 (br s, 1H).

[0165] To a solution of compound **2** (18.0 g, 83.2 mmol, 1.0 eq) in EtOH (200 mL) was added hydrazine monohydrate (16.7 g, 333 mmol, 4.0 eq) in one portion at 25 °C. The mixture was stirred at 80 °C for 16 h. TLC showed the reaction was completed. The mixture was cooled to 25 °C and concentrated under reduced pressure at 40 °C. The residue was purified by silica gel chromatography (1:10 MeOH/EtOAc) to afford **3** (14.0 g, 69.2 mmol, 83% yield) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 7.35 - 7.42 (m, 1H), 7.43 - 7.51 (m, 2H), 7.73 (s, 1H), 7.99 - 8.06 (m, 1H), 8.97 (br s, 1H).

[0166] To a solution of compound **3** (14.0 g, 69.2 mmol, 1.0 *eq)* in THF (120 mL) was added a solution of isocyanatocyclopropane (28.8 g, 346 mmol, 5.0 *eq)* in DCM (500 mL) dropwise at 25 °C. The mixture was stirred at 25 °C for 2h. The resulting yellow precipitate was filtered and washed with EtOAc (200 mL) to afford **4** (14.0 g, 49.1 mmol, 70% yield): ESI *m*/*z* 286.1[M + 1]$^+$.

[0167] To a solution of compound **4** (14 g, 49.07 mmol, 1.0 eq) in H_2O (300 mL) was added NaOH (5.89 g, 147.21 mmol, 3.0 eq) in one portion at 25 °C. Then the reaction mixture was heated at 100 °C. After 40 h, TLC showed the reaction was completed and the mixture was cooled to 25 °C. 3N HCl was added and at pH 5-6, a crystalline solid formed. The solid was isolated by filtration, washed with water (30 mL) and dried at 50 °C to afford **5** (8 g, 29.93 mmol, 61% yield): ^{1}H NMR (400 MHz, DMSO-d6) δ 0.80 - 0.90 (m, 2H), 0.93 - 1.04 (m, 2H), 3.13 (dt, J=6.90, 3.33 Hz, 1H), 7.42 - 7.61 (m, 2H), 7.91 (s, 1H), 8.10 (d, J=7.40 Hz, 2H).

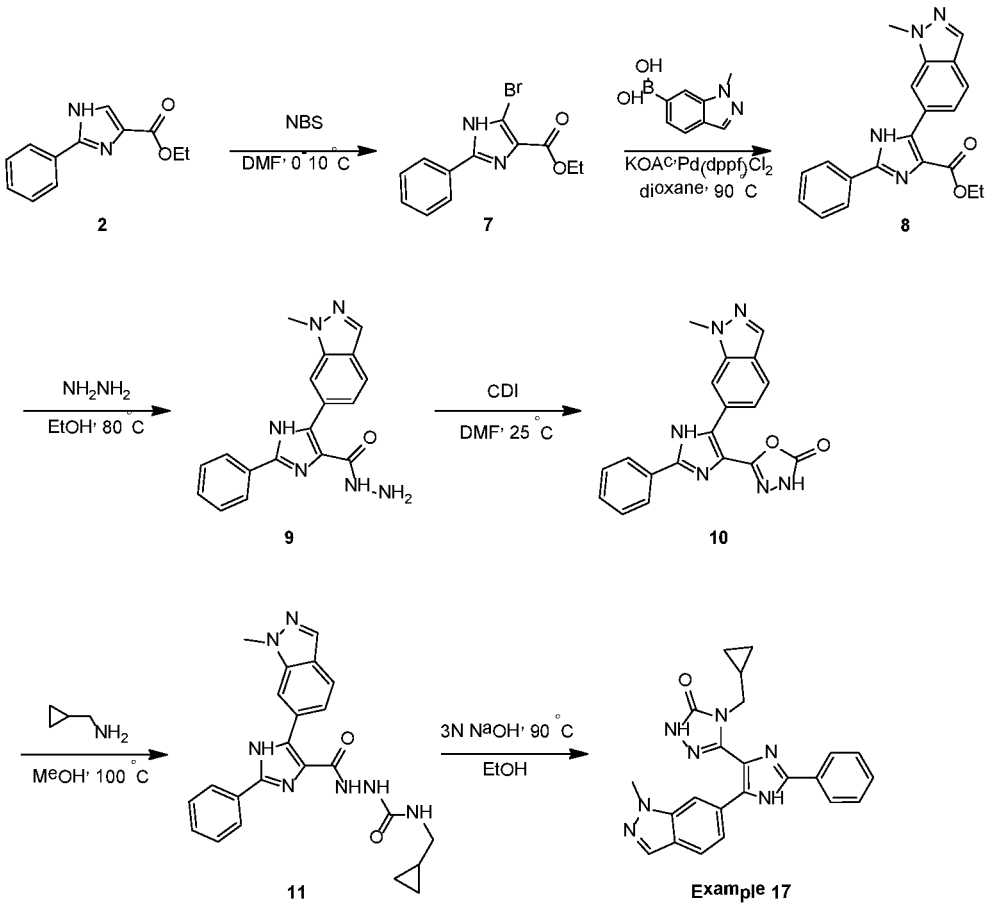
[0168] To a solution of compound **5** (8.00 g, 29.9 mmol, 1.0 eq) in DMF (60 mL) was added NBS (6.39 g, 35.9 mmol, 1.2 eq) in portions at 0 °C under N_2 atmosphere. The resulting mixture was stirred at 0-10 °C for 30 min. TLC showed the reaction was complete. The reaction mixture was quenched with water (50 mL) and the aqueous phase was extracted with ethyl acetate (6 x 100 mL). The combined organic layers were washed with sat. sodium thiosulfate (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel chromatography (PE/EtOAc, 50-100%) to afford **6** (5.50 g, 15.9 mmol, 53 % yield) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 0.62 (br s, 2H), 0.78 - 0.87 (m, 2H), 2.97 (br s, 1H), 7.43 - 7.57 (m, 3H), 7.97 (d, *J*=7.15 Hz, 2H).

[0169] Compound **6** (50 mg, 0.14 mmol, 1.0 eq), (3-acetylphenyl)boronic acid (45.9 mg, 0.280 mmol, 2.0 eq), K_2CO_3 (40 mg, 0.28 mmol, 2.0 eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (24 mg, 0.03 mmol, 0.20 eq) in dioxane (2 mL) and H_2O (0.5 mL) was degassed with nitrogen and then heated at 90 °C for 3 h under nitrogen atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was cooled to 25 °C and the solvent was removed *in vacuo.* The residue was dissolved in MeOH (10 mL) and filtered. The resulting filtrate was concentrated and purified by prep-HPLC (HCl buffer) to afford 3-(5-(3-acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride **(Example 1)** (12 mg, 31.1 umol, 22% yield) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 0.63 - 0.83 (m, 4H), 2.47 (dt, *J*=7.15, 3.33 Hz, 1H), 2.67 (s, 3H), 7.60 - 7.74 (m, 4H), 7.87 - 7.97 (m, 1H), 8.03 - 8.17 (m, 3H), 8.37 (t, *J*=1.57 Hz, 1H); ESI *m*/*z* 386.2[M + 1]$^+$.

General Procedure B:

Example 17: 4-(Cyclopropylmethyl)-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one)

[0170]



2 7 8 9 10 11 Example 17

[0171] To a solution of compound **2** (2.00 g, 9.25 mmol, 1.00 *eq)* in DMF (20 mL), was added NBS (1.98 g, 11.10 mmol, 1.20 *eq)* in portions at 0 °C under nitrogen. The mixture was stirred at 0-10 °C for 30 min. The mixture was diluted with water and the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic fractions were washed with a solution of saturated sodium thiosulfate (30 mL), dried with anhydrous sodium sulfate and concentrated under vacuum to afford 7 (1.83 g, 6.20 mmol, 67% yield) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 1.34 (t, *J*=7.16 Hz, 3H) 4.33 (q, *J*=6.97 Hz, 2H) 7.49 (d, *J*=6.41 Hz, 3H) 8.09 (d, *J*=6.40 Hz, 2H) 13.51 - 13.85 (m, 1H).

[0172] To a mixture of compound **7** (800 mg, 2.71 mmol, 1.00 eq) and (1-methylindazol-6-yl)boronic acid (477 mg, 2.71 mmol, 1.00 eq) in dioxane (10 mL) was added KOAc (266.03 mg, 2.71 mmol, 1.00 eq) and Pd(dppf)Cl_2 (198 mg, 271 umol, 0.10 eq) in one portion at 25 °C under nitrogen. Then the mixture was heated to 90 °C and stirred for 16 hr. The mixture was concentrated under reduced pressure and the residue was filtered through silica gel (0-100% EtOAc in PE). The crude product was purified by preparative HPLC to afford **8** (480 mg, 1.39 mmol, 51% yield) as a yellow solid: ESI m/z 347.1[M + 1]$^+$.

[0173] To a mixture of compound **8** (450 mg, 1.30 mmol, 1.00 eq) in EtOH (5 mL) was added hydrazine hydrate (976 mg, 19.5 mmol, 15.0 eq) in one portion at 25 °C under nitrogen. Then the reaction mixture was stirred at 80 °C for 30 hours. The mixture was concentrated and the residue was taken up in EtOAc (10 mL). The suspention was stirred for 10 min and filtered to afford 9 (300 mg, 902 umol, 69% yield) as a gray solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 4.09 (s, 3H) 4.51 (br. s., 2H) 7.42 - 7.55 (m, 3H) 7.64 (d, *J*=8.67 Hz, 1H) 7.76 - 7.84 (m, 1H) 8.07 - 8.23 (m, 4H) 9.15 (br. s., 1H) 12.94 (br. s., 1H).

[0174] To a mixture of compound **9** (50 mg, 150 umol, 1.00 eq) in DMF (1.0 mL) was added carbonyldiimidazole (29 mg, 180 umol, 1.2 eq) in one portion at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 16 hr and was concentrated in vacuum. The residue was taken up in water (5 mL) and stirred for 15 min. The precipitate was filtered and dried under vacuum to afford **10** (35 mg, 97 umol, 64% yield) as a gray solid: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 4.10 (s, 3H) 7.03 (s, 2H) 7.42 - 7.57 (m, 4H) 7.86 (br. s., 1H) 8.11 (d, *J*=13.43 Hz, 4H) 13.08 - 13.36 (m, 1H).

[0175] Compound **10** (35 mg, 97 umol, 1.00 eq) and cyclopropylmethanamine (69 mg, 976 umol, 10.0 eq) were taken up in MeOH (2.0 mL) in a microwave tube. The sealed tube was irradiated in the microwave at 90 °C for 1.5 hr. The reaction mixture was concentrated under vacuum to afford 11 (30 mg, 70 umol, 72% yield) as yellow solid: ESI *m/z* 430.2 [M + 1]$^+$.

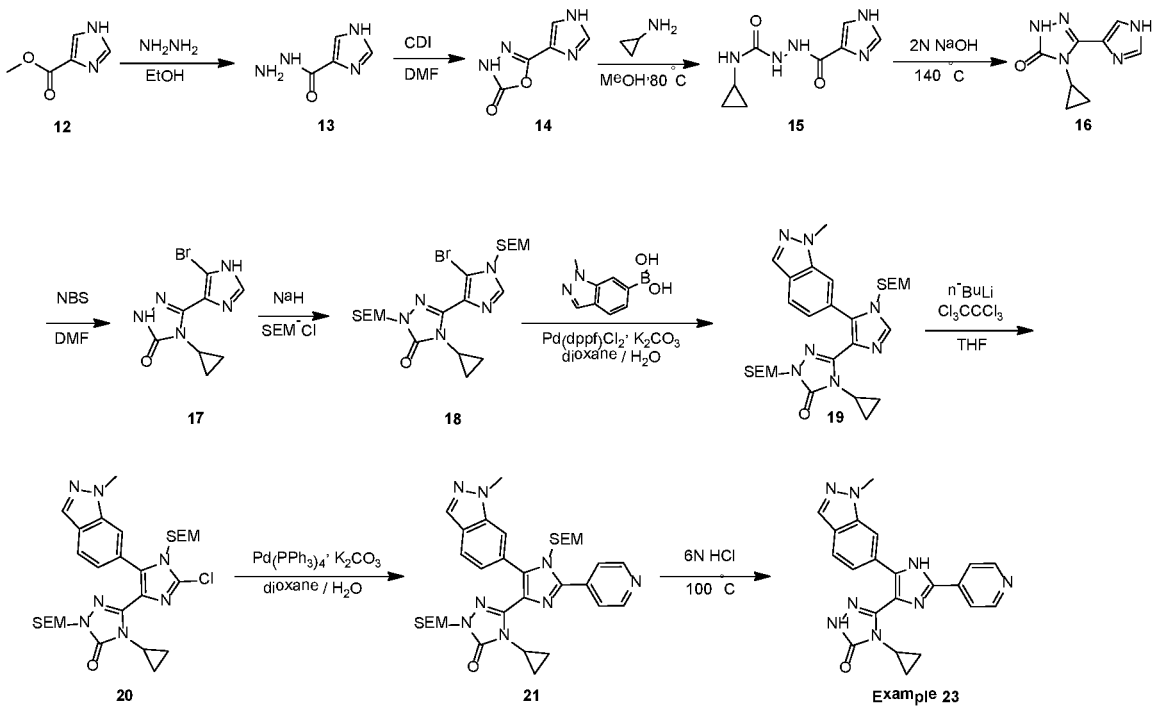
[0176] To a mixture of compound **11** (20 mg, 47 umol, 1.0 eq) in EtOH (1.0 mL) was added NaOH (3M, 16 uL, 1.0 eq)

in one portion at 25 °C under nitrogen. The reaction mixture was stirred at 90 °C for 16 hr. 3N HCl was added to lower the pH to 5-6 which caused a precipitate to form. The solid was isolated by filtration and taken up in DMF (5 mL) for purification by preparative HPLC. 4-(Cyclopropylmethyl)-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one **(Example 17)** (13 mg, 32 umol, 68% yield) was isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.08 - 0.41 (m, 4H) 3.67 (br. s., 2H) 4.08 (s, 3H) 7.33 - 7.49 (m, 2H) 7.51 - 7.57 (m, 2H) 7.80 (d, *J*=8.41 Hz, 1H) 8.03 - 8.09 (m, 2H) 8.10 - 8.14 (m, 2H) 11.79 (br. s., 1H); ESI *m/z* 412.1[M + 1]$^+$.

General Procedure C:

Example 23: 4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one

[0177]



[0178] A solution of compound **12** (18.0 g, 142.7 mmol, 1.0 eq) and hydrazine hydrate (35.7 g, 713.7 mmol, 5.0 *eq)* in EtOH (200 mL) was stirred at 90 °C for 15 h. After cooling to room temperature, a precipitate formed. The solid was filtered, and dried under vacuum to afford compound **13** (15.0 g, 119 mmol, 83% yield) as a white crystalline solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (br. s., 2H) 7.61 (s, 1H) 7.72 (d, *J*=0.88 Hz, 1H) 9.10 (br. s., 1H) 12.49 (br. s., 1H).

[0179] Carbonyldiimidazole (17.7 g, 109.4 mmol, 1.2 eq) was added to a suspension of compound **13** (11.5 g, 91.2 mmol, 1.0 *eq)* in DMF (110 mL) at 0 °C. Initially, the solution cleared, but after stirring at 15 °C for 3 hr, a precipitate formed. The solid was filtered, washed with DCM (100 mL) and dried under vacuum to afford compound **14** (10.4 g, 67.7 mmol, 74% yield) as an off-white solid: ESI *m/z* 153.0[M+1]$^+$.

[0180] A clear solution of compound **14** (5.00 g, 32.87 mmol, 1.00 eq) and cyclopropanamine (9.38 g, 164.4 mmol, 5.0 *eq)* in MeOH (5.00 mL) was stirred under microwave irradiation at 80 °C for 2 hr. After cooling, a precipitate formed. The reaction mixture was concentrated and the residue was triturated in ethyl acetate (40 mL). The solid was filtered and dried under vacuum to afford compound **15** (4.50 g, 21.5 mmol, 65% yield) as a light-yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34 - 0.42 (m, 2H) 0.52 - 0.61 (m, 2H) 2.42 - 2.49 (m, 1H) 6.49 (br. s., 1H) 7.71 (s, 1H) 7.75 (s, 2H) 9.34 (br. s., 1H) 12.53 (br. s., 1H).

[0181] A clear solution of compound **15** (4.70 g, 22.5 mmol, 1.0 *eq)* in 2N NaOH (13 mL) was stirred under microwave irradiation at 140 °C for 4 hr. The reaction mixture was cooled to 0 °C, and conc. HCl was added to adjust the pH to 8. The precipitate was filtered, washed with water (100 mL) and dried under vacuum to afford compound **16** (2.90 g, 14.6 mmol, 65.1% yield, 96.4% purity) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 - 0.90 (m, 4H) 3.01 - 3.09 (m, 1H) 7.64 (s, 1H) 7.80 (s, 1H) 11.52 (s, 1H) 12.50 (br. s., 1H); ESI *m/z* 192.1 [M+1]$^+$.

[0182] *N*-Bromosuccinimide (5.36 g, 30.1 mmol, 1.2 eq) was added in portions to a 0 °C solution of compound **16**

(4.80 g, 25.1 mmol, 1.0 *eq)* in DMF (40 mL) over 1 hr. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was purified by p-HPLC directly to afford compound **17** (4.60 g, 12.0 mmol, 48% yield) as a white crystalline TFA salt: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.51 - 0.61 (m, 2H) 0.73 - 0.83 (m, 2H) 2.85 - 2.95 (m, 1H) 7.94 (s, 1H) 11.97 (s, 1H); ESI *m*/*z* 270.0, 272.0 [M+1]$^+$.

[0183] A solution of compound **17** (4.50 g, 11.7 mmol, 1.0 *eq)* in DMF (2 mL) was added dropwise to another solution of SEM-Cl (5.86 g, 35.2 mmol, 3.0 *eq)* in THF (50 mL) at 0 °C. Then the solution was stirred at 10 °C for 1 hr at which time a precipitate formed. Sodium hydride (1.88 g, 46.9 mmol, 4.0 *eq)* was added to the mixture in portions. Initially, the reaction mixture turn red, but the color faded as it was stirred for 15 hr. The reaction was quenched by the dropwise addition of water (10 mL) at 0 °C. Additional water (100 mL) was added and the the pH was adjusted to 7 with aq. HCl. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic fractions were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (10-50% EA in PE) to afford compound **18** (2.90 g, 5.47 mmol, 46.7% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H) 0.02 (s, 9H) 0.63 - 0.78 (m, 2H) 0.78 - 0.94 (m, 4H) 0.94 - 1.02 (m, 2H) 3.03 - 3.11 (m, 1H) 3.39 - 3.48 (m, 2H) 3.63 - 3.74 (m, 2H) 5.21 (s, 2H) 5.33 (br. s., 2H) 7.68 (s, 1H); ESI *m*/*z* 532.1, 530.1 [M+1]$^+$.

[0184] Compound **18** (1.50 g, 2.83 mmol, 1.0 *eq),* (1-methylindazol-6-yl)boronic acid (697 mg, 3.96 mmol, 1.40 *eq),* K_2CO_3 (782 mg, 5.66 mmol, 2.0 *eq)* and Pd(dppf)Cl_2 (207 mg, 283 umol, 0.10 *eq)* were combined in a mixed solvent of dioxane (20 mL) and water (5 mL). The reaction mixture was degassed with nitrogen and then heated at 90 °C for 15 hr under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (0-100% EA in DCM) to afford compound **19** (1.46 g, 80% purity) as a brown oil: ESI *m*/*z* 582.3 [M+1]$^+$.

[0185] n-BuLi (2.5 M, 1.81 mL, 1.80 eq) was added to a solution of compound **19** (1.46 g, 2.51 mmol, 1.00 *eq)* in THF (33 mL) at -78 °C under a nitrogen atmosphere. The resulting slurry was stirred at - 78 °C for 5 min, then a solution of 1,1,1,2,2,2-hexachloroethane (832 mg, 3.51 mmol, 1.40 *eq)* in THF (3 mL) was added in portions. The reaction mixture was stirred for 30 min at -78 °C as the color turned from brown to red. The reaction was quenched by the addition of water (40 mL) at 0 °C and the reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic fractions were washed with brine (50 mL), concentrated and the residue was purified by column chromatography (20%-100% EA in PE) to afford compound **20** (1.05 g, 85% purity) as a red gum: ESI *m*/*z* 616.2 [M+1]$^+$.

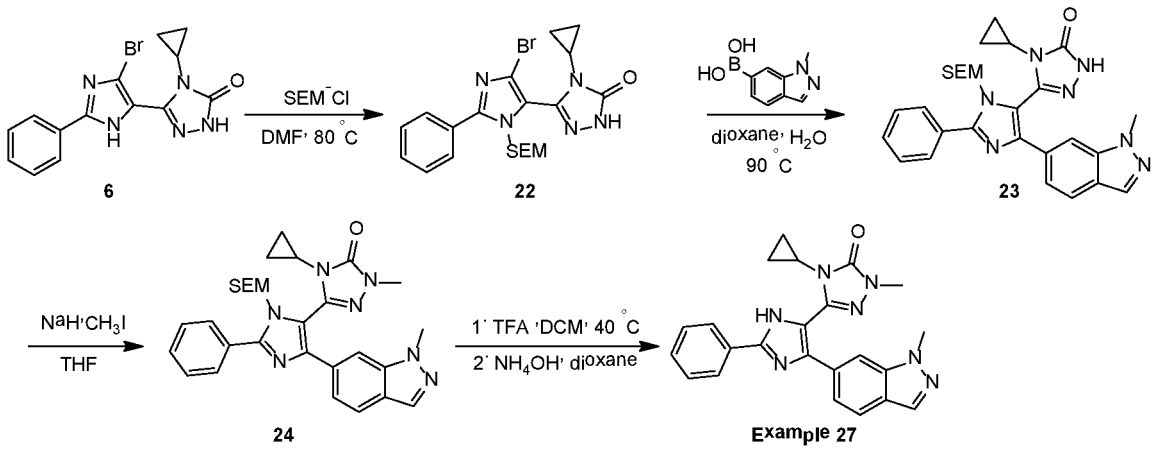
[0186] Compound **20** (100 mg, 162 umol, 1.0 *eq),* 4-pyridylboronic acid (40 mg, 325 umol, 2.0 *eq),* K_2CO_3 (45 mg, 325 umol, 2.0 eq) were combined in a mixed solvent of dioxane (3 mL) and water (600 uL). Pd(PPh_3)$_4$ (19 mg, 16 umol, 0.10 eq) was added under nitrogen atmosphere, and then the mixture was stirred at 95 °C for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (0-10% MeOH in DCM) to afford compound **21** (80 mg) as a yellow oil: ESI *m*/*z* 659.2 [M+1]$^+$.

[0187] A solution of compound **21** (80 mg) in 6M hydrochloric acid (10 mL) was heated to 100 °C for 3 hr. The reaction mixture was concentrated and the residue was triturated in methanol (2 mL). The solid was isolated by filtration to give 4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride **(Example 23)** (23 mg, 58 umol, 48% yield) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.59 - 0.74 (m, 4H) 4.09 (s, 3H) 7.34 (d, *J*=8.67 Hz, 1H) 7.44 - 7.68 (m, 1H) 7.84 (d, *J*=8.48 Hz, 1H) 8.04 - 8.21 (m, 2H) 8.54 (d, *J*=5.46 Hz, 2H) 8.94 (d, *J*=6.40 Hz, 2H) 11.94 (br. s., 1H);ESI *m*/*z* 399.1 [M+1]$^+$.

General Procedure D:

Example 27: 4-Cyclopropyl-2-methyl-5-[4-(1-methylindazol-6-yl)-2-phenyl-1H-imidazol-5-yl]-1,2,4-triazol-3-one

[0188]



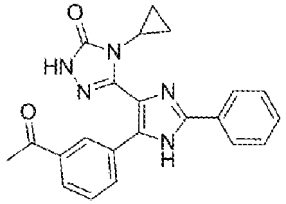
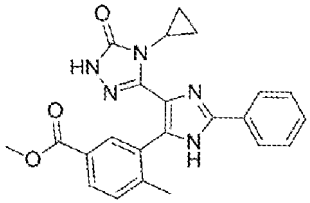
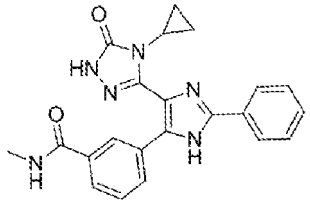
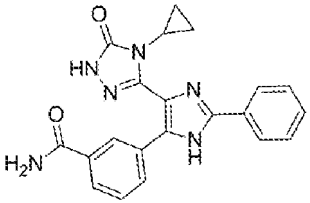
[0189] SEM-Cl (188 mg, 1.13 mmol, 1.95 eq) was added to a solution of compound **6** (200 mg, 578 umol, 1.0 eq) and TEA (146 mg, 1.44 mmol, 2.5 eq) in DMF (6 mL). The reaction mixture was purged with nitrogen and heated at 80 °C for 2 h. The yellow mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20-50% EA in PE) to afford **22** (161 mg) as yellow solid: ESI *m/z* 477.9[M + 1]$^+$.

[0190] Compound **22** (50 mg, 105 umol, 1.0 eq) and (1-methylindazol-6-yl)boronic acid (26.04 mg, 147.98 umol, 1.41 eq) were combined in 1,4-dioxane (2 mL) and water (400 uL). K_2CO_3 (30 mg, 217 umol, 2.1 eq) and $Pd(PPh_3)_4$ (18 mg, 16 umol, 0.15 eq) were added and the mixture was purged with nitrogen. The reaction mixture was heated at 90 °C for 20 h. The residue was purified by prep-TLC (5% MeOH in DCM) to afford **23** (38 mg, 67 umol, 64% yield) as yellow solid: ESI *m/z* 528.2[M + 1]$^+$.

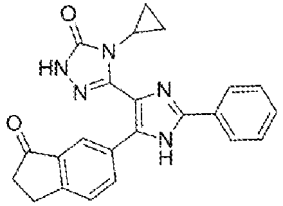
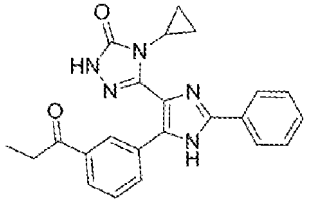
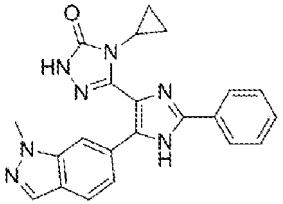
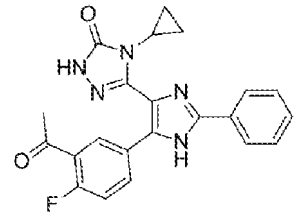
[0191] Sodium hydride (4 mg, 100 umol, 1.5 eq) was added to a solution of compound **23** (38 mg, 67 umol, 1.0 eq) in THF (3 mL) at -10 °C and the reaction was stirred for 1 hr at -10 °C. Iodomethane (610 mg, 4.30 mmol, 64.1 eq) was added dropwise and the reaction mixture was purged with nitrogen. After stirring for 16 hr at 15 °C, the mixture was cooled to 0 °C and quenched with ice-water (15 mL). The reaction mixture was stirred for another 0.5 h and was extracted with DCM (2 x 10 mL). The combined organic fractions were washed with brine (2 x 10 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (10% MeOH in DCM) to afford **24** (36 mg) as yellow solid: ESI *m/z* 542.2[M + 1]$^+$.

[0192] To a solution of compound **24** (20 mg, 37 umol, 1.0 eq) in DCM (10 mL) was added TFA (3 mL) at 14 °C. The reaction mixture was heated at 40 °C for 1 hr and concentrated under reduced pressure. The residue was taken up in dioxane (3 mL), then ammonium hydroxide (1.29 mg, 36.9 umol, 1.0 eq) was added dropwise. The mixture was stirred at 14 °C for 0.5 h and was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 4-cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride **(Example 27)** (3 mg, 7.3 umol, 20% yield) as light yellow solid: ^{1}H-NMR(DMSO-d_6, 300 MHz): δ 8.17 (d, J=7.3 Hz, 2H), 8.09 (d, J=9.2 Hz, 2H), 7.77-7.85 (m, 1H), 7.44-7.62 (m, 3H), 7.27-7.34 (m, 1H), 4.08 (s, 3H), 3.39 (s, 3H), 1.12-1.27 (m, 1H), 0.63 ppm (d, J=4.5 Hz, 4H); ESI *m/z* 412.0 [M+1]$^+$.

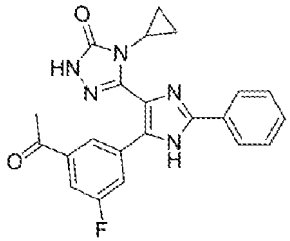
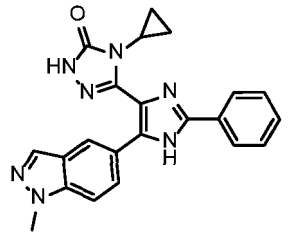
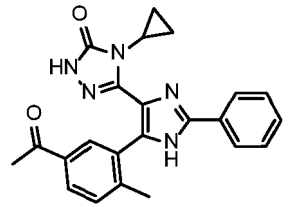
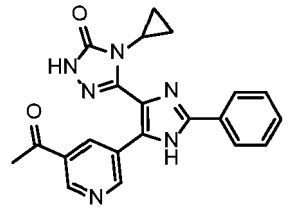
Table 2: Example Compounds

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
1	3-(5-(3-acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ 0.63 - 0.83 (m, 4H), 2.47 (dt, *J*=7.15, 3.33 Hz, 1H), 2.67 (s, 3H), 7.60 - 7.74 (m, 4H), 7.87 - 7.97 (m, 1H), 8.03 - 8.17 (m, 3H), 8.37 (t, *J*=1.57 Hz, 1H); ESI *m/z* 386.2[M + 1]$^+$.	22%
2	methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methyl benzoate hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ0.72 - 0.79 (m, 2H), 0.80 - 0.87 (m, 2H), 2.20 - 2.29 (m, 1H), 2.41 (s, 3H), 3.93 (s, 3H), 7.57 (d, J=8.03 Hz, 1H), 7.65 - 7.74 (m, 3H), 8.06 (dd, J=7.53, 2.01 Hz, 2H), 8.10 (dd, J=8.03, 1.76 Hz, 1H), 8.16 (d, J=1.63 Hz, 1H); ESI *m/z* 416.1[M + 1]$^+$.	22%
3	3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methyl benzamide hydrochloride		A	^{1}H NMR (400 MHz,CD_3OD) δ 0.64-0.84 (m, 4H), 2.22 - 2.36 (m, H), 2.97 (s, 3H), 7.63 - 7.80 (m, 4H), 7.83 - 7.89 (m, 1H), 8.00 (d, *J*=7.91 Hz, 1H), 8.10 (dd, *J*=8.09, 1.44 Hz, 2H), 8.23 (t, *J*=1.57 Hz, 1H); ESI *m/z* 401.1[M + 1]$^+$.	28 %
4	3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl) benzamide hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ0.65 - 0.82 (m, 4H), 2.24 - 2.36 (m, 1H), 3.33 (dt, J=3.26, 1.63 Hz, 4H), 7.63 - 7.82 (m, 4H), 7.85 - 7.95 (m, 1H), 8.04 - 8.19 (m, 3H), 8.29 (t, *J*=1.57 Hz, 1H); ESI *m/z* 387.1[M + 1]$^+$.	22%

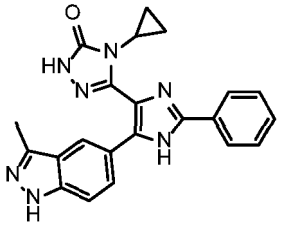
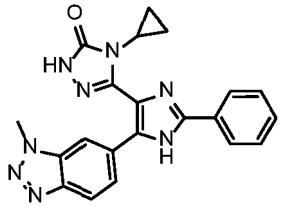
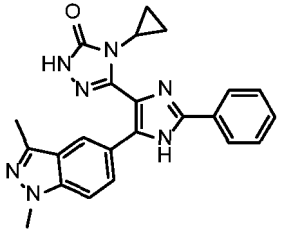
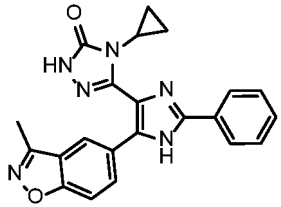
(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
5	4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ0.59 - 0.88 (m, 4H), 2.35 (dt, J=7.03, 3.39 Hz, 1H), 2.72 - 2.88 (m, 2H), 3.23 - 3.31 (m, 2H), 7.66 - 7.83 (m, 4H), 7.96 (dd, J=7.97, 1.82 Hz, 1H), 8.03 - 8.17 (m, 3H); ESI *m/z* 397.1[M + 1]$^+$.	16%
6	4-cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ 0.64 - 0.82 (m, 4H), 1.22(t, *J*=7.15 Hz, 3H), 2.50 (tt, *J*=7.07, 3.65 Hz, 1H) 3.11 (q, *J*=7.15 Hz, 2H), 7.58 - 7.70 (m, 4H), 7.90(d, *J*=7.78 Hz, 1H), 8.01-8.15 (m, 3H), 8.35 (s, 1H);ESI *m/z* 400[M + 1]$^+$	63%
7	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, DMSO-d_6) 60.61 - 0.70 (m, 4H) 4.10 (s, 3H) 7.30 (dd, *J*=8.41, 1.13 Hz, 1H) 7.51 - 7.69 (m, 3H) 7.83 (d, *J*=8.53 Hz, 1H) 8.07 - 8.20 (m, 2H) 8.26 (d, *J*=6.90 Hz, 2H) 12.08 (s, 1H); ESI m/z 398.2[M + H]$^+$.	4%
8	3-(5-(3-acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ 0.67 - 0.74 (m, 2H), 0.76 - 0.84 (m, 2H), 2.45 (dt, *J*=6.93, 3.37 Hz, 1H), 2.69 (d, *J*=4.64 Hz, 3H), 7.50 (dd, *J*=10.67, 8.66 Hz, 1H), 7.69 - 7.80 (m, 4H), 7.90 - 8.01 (m, 1H), 8.09 (d, *J*=6.78 Hz, 2H), 8.27 (dd, *J*=6.71, 2.45 Hz, 1H);ESI m/z 404[M + 1]$^+$.	29%

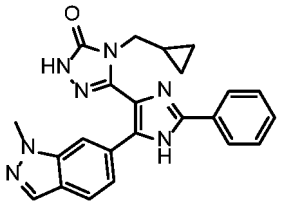
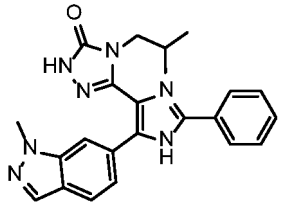
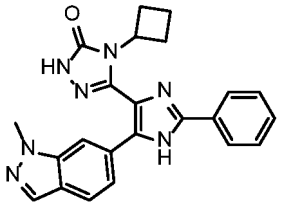
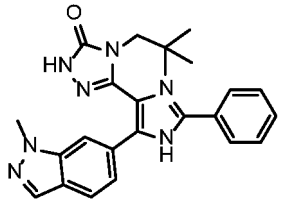
(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
9	3-(5-(3-acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.61 - 0.73 (m, 4H) 2.62 (s, 3H) 2.81 (dt, *J*=7.15, 3.33 Hz, 1H) 7.45 - 7.59 (m, 3H) 7.73 (dt, *J*=9.25, 1.90 Hz, 1H) 7.86 - 7.91 (m, 1H) 8.11 - 8.19 (m, 3H) 11.98 - 12.10 (m, 1H); ESI m/z 404.1[M + 1]$^+$	13%
10	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD) δ 0.63 - 0.76 (m, 4H) 2.03 - 2.16 (m, 1H) 4.15 (s, 3H) 7.67 - 7.86 (m, 5H) 8.08 - 8.15 (m, 2H) 8.19 (s, 2H); ESI *m/z* 398.0[M+1]$^+$	54%
11	3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one hydrochloride		A	^{1}HNMR (400 MHz, DMSO-d_6) δ 0.64 - 0.84 (m, 4 H) 2.28 (s, 3 H) 2.58 (s, 3 H) 7.45 - 7.61 (m, 4 H) 7.90 - 8.00 (m, 2 H) 8.11 (d, J=7.28 Hz, 2 H) 11.73 (br. s., 1 H) ESI *m/z* 400.0 [M+1]$^+$	43%
12	3-(5-(5-acetylpyridin-3-yl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one formate		A	^{1}H NMR (300 MHz, DMSO-d_6) δ 0.61 - 0.77 (m, 1 H) 2.67 (s, 3 H) 2.79 - 2.96 (m, 1 H) 7.41 - 7.59 (m, 3 H) 8.11 (d, *J*=7.16 Hz, 2 H) 8.37 (br. s., 1 H) 8.62 (s, 1 H) 8.96 - 9.16 (m, 2 H) 11.89 (br. s., 1 H); ESI m/z 387.0[M+1]$^+$	22%

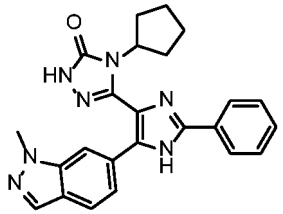
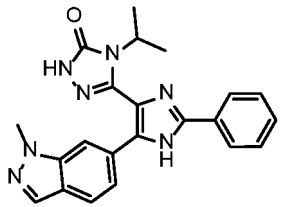
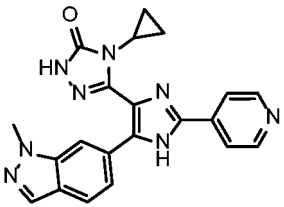
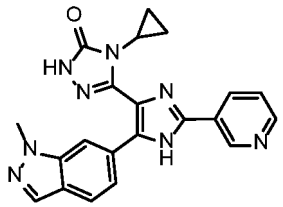
(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
13	4-cyclopropyl-3-(5-(3-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one hydrochloride		A	^{1}HNMR (400 MHz, DMSO-d_6) δ 0.63 (d, J=4.52 Hz, 4H) 2.60 - 2.66 (m, 1H) 7.45 - 7.59 (m, 5H) 8.15 (s, 1H) 8.22 (d, J=7.40 Hz, 2H) 11.94 (br. s., 1H) 12.87 (br. s., 1H); ESI *m/z* 398.4[M+1]$^+$	35%
14	4-cyclopropyl-3-(5-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		A	^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.90-12.05 (m, 1H), 8.22-8.33 (m, 1H), 8.11-8.21 (m, 2H), 7.99-8.11 (m, 1H), 7.56 (t, J=7.4 Hz, 4H), 4.34 (br. s., 3H), 2.63-2.68 (m, 1H), 0.64 ppm (br. s., 4H); ESI m/z 399.1[M+1]$^+$	31%
15	4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5 (4H)-one hydrochloride		A	^{1}H NMR (400 MHz, CD_3OD): δ 8.16-8.23 (m, 1H), 8.08-8.15 (m, 2H), 7.70-7.81 (m, 3H), 7.61-7.70 (m, 2H), 4.05 (s, 3H), 2.60 (s, 3H), 2.09-2.20 (m, 1H), 0.62-0.75 (m, 4H); ESI *m/z* 412.0[M+1]$^+$	13%
16	4-cyclopropyl-3-(5-(3-methylbenzo[d]isoxazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5 (4H)-one		A	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.15 (m, 1H), 8.00-8.07 (m, 2H), 7.81-7.86 (m, 1H), 7.63-7.70 (m, 1H), 7.44-7.58 (m, 3H), 2.61 (s, 4H), 0.62-0.80 (m, 4H); ESI *m/z* 399.1[M + 1]$^+$	2%

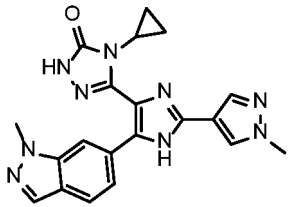
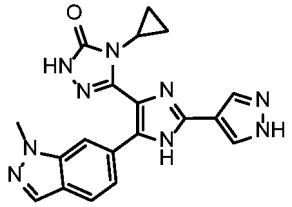
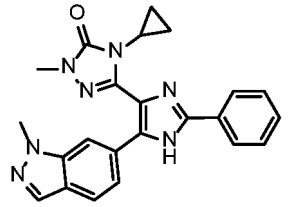
(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
17	4-(cyclopropylmethyl)-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.08 - 0.41 (m, 4H) 3.67 (br. s., 2H) 4.08 (s, 3H) 7.33 - 7.49 (m, 2H) 7.51- 7.57 (m, 2H) 7.80 (d, *J*=8.41 Hz, 1H) 8.03 - 8.09 (m, 2H) 8.10 - 8.14 (m, 2H) 11.79 (br. s., 1H); ESI *m/z* 412.1[M + 1]$^+$	68%
18	4-isobutyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (d, *J*=6.65 Hz, 6H) 1.87 - 2.07 (m, 1H) 3.66 (br. s., 2H) 4.00 (s, 3 H) 7.12 (br. s., 1H) 7.31 (br. s., 2H) 7.48 - 7.70 (m, 2H) 7.90 (br. s., 1H) 8.02 - 8.11 (m, 3H) 11.26 - 11.47 (m, 1H); ESI *m/z* 414.2 [M+1]$^+$	44%
19	4-cyclobutyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, DMSO-d_6) δ1.40 - 1.62 (m, 2H) 1.83 (br. s., 2H) 2.79 (br. s., 2H) 4.03 (s, 3H) 4.51 (br. s., 1H) 7.19 - 7.53 (m, 4H) 7.67 (d, *J*=8.16 Hz, 1H) 7.88 - 8.04 (m, 2H) 8.10 (d, *J*=7.40 Hz, 2H) 11.67 (br. s., 1H) 13.21 (s, 1H); ESI *m/z* 412.2[M+H]$^+$	50%
20	3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-4-neopentyl-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, CD_3OD) δ 0.72 (s, 9H) 3.62 (br. s., 2H) 4.13 (s, 3H) 7.42 (dd, *J*=8.47, 1.19 Hz, 1H) 7.50 (d, *J*=7.15 Hz, 1H) 7.52-7.58 (m, 2H) 7.83 (d, *J*=8.53 Hz, 1H) 8.01 (s, 1H) 8.04 - 8.09 (m, 3H); ESI *m/z* 428.3[M+1]$^+$	17%

(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
21	4-cyclopentyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, CD_3OD) δ 1.37 - 1.50 (m, 2H) 1.61 (br.s., 2H) 1.72 (br.s., 2H) 2.03 (dd, *J*=12.86, 8.22 Hz, 2H) 4.11 (s, 3H) 4.24 (t, *J*=8.78 Hz, 1H) 7.32 (d, *J*=8.41 Hz, 1H) 7.47-7.59 (m, 3H) 7.80 - 7.89 (m, 2H) 8.03 - 8.10 (m, 3H) ; ESI m/z 426 $[M+1]^+$	7%
22	4-isopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one		B	^{1}H NMR (400 MHz, CD_3OD) δ 1.28 (d, *J*=6.78 Hz, 6H) 4.12 (s, 3H) 4.14 - 4.19 (m, 1H) 7.34 (dd, *J*=8.41, 1.38 Hz, 1H) 7.47 - 7.58 (m, 3H) 7.83 (d, *J*=8.78 Hz, 1H) 7.91 (s, 1H) 8.02 - 8.10 (m, 3 H); ESI *m/z* 400.3$[M + 1]^+$	10%
23	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride		C	^{1}H NMR (300 MHz, DMSO-d_6) δ 0.59 - 0.74 (m, 4H) 4.09 (s, 3H) 7.34 (d, *J*=8.67 Hz, 1H) 7.44 - 7.68 (m, 1H) 7.84 (d, *J*=8.48 Hz, 1H) 8.04 - 8.21 (m, 2H) 8.54 (d, *J*=5.46 Hz, 2H) 8.94 (d, *J*=6.40 Hz, 2H) 11.94 (br. s., 1H);ESI *m/z* 399.1 $[M+1]^+$	48%
24	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride		C	^{1}H NMR (400 MHz, CD_3OD) δ 0.64 - 0.79 (m, 4H) 2.36 - 2.54 (m, 1H) 4.16 (s, 3H) 7.42 (dd, J=8.41, 1.25 Hz, 1H) 7.91 (d, J=8.28 Hz, 1H) 8.10 (s, 1H) 8.13 (s, 1H) 8.31 (dd, J=8.22, 5.83 Hz, 1H) 9.00 (d, J=5.27 Hz, 1H) 9.28 (d, J=8.28 Hz, 1H) 9.61 (s, 1H); ESI *m/z* 399.2 $[M+1]^+$	42%

(continued)

Example	Chemical Name	Structure	General Procedure	Characterization	Yield
25	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		C	^{1}H NMR (400 MHz, CD_3OD) δ 0.63 - 0.73 (m, 4H) 2.08 - 2.24 (m, 1H) 4.09 (s, 3H) 4.16 (s, 3H) 7.36 (d, J=8.41 Hz, 1H) 7.96 (d, J=8.41 Hz, 1H) 8.05 (s, 1H) 8.13 (s, 1H) 8.27 (s, 1H) 8.54 (s, 1H); ESI *m/z* 402.2 $[M+1]^+$	38%
26	4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		C	^{1}H NMR (400 MHz, CD_3OD) δ 0.60 - 0.76 (m, 4H) 2.07 - 2.18 (m, 1H) 4.16 (s, 3H) 7.34 - 7.40 (m, 1H) 7.97 (d, J=8.41 Hz, 1H) 8.02 (s, 1H) 8.14 (d, J=0.75 Hz, 1H) 8.47 (s, 2H); ESI *m/z* 388.0 $[M+1]^+$	36%
27	4-cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride		D	^{1}H-NMR(DMSO-d_6, 300 MHz): δ 8.17 (d, J=7.3 Hz, 2H), 8.09 (d, J=9.2 Hz, 2H), 7.77-7.85 (m, 1H), 7.44-7.62 (m, 3H), 7.27-7.34 (m, 1H), 4.08 (s, 3H), 3.39 (s, 3H), 1.12-1.27 (m, 1H), 0.63 ppm (d, J=4.5 Hz, 4H); ESI *m/z* 412.0 $[M+1]^+$	20%

Example 28: Inhibition of tetra-acetylated histoneH4 binding individual BET Bromodomains

[0193] Proteins were cloned and overexpressed with a *N*-terminal 6xHis 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 Ni-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.

[0194] Binding of tetra-acetylated histone H4 peptide (Millipore) and BET bromodomains was confirmed by Amplified Luminescent Proximity Homogenous Assay (AlphaScreen). N-terminally His-tagged bromodomains (BRD4(1) at 20 nM and BRD4(2) at 100nM) and biotinylated tetra-acetylated histone H4 (10-25 nM) were incubated in the presence of nickel chelate acceptor beads and streptavidin donor beads (PerkinAlmer, 6760000K) added to a final concentration of 2 μg/ml under green light in a white 96 well microtiter plate (Greiner). For inhibition assays, serially diluted compounds were added to the reaction mixtures in a 0.1% final concentrations of DMSO. Final buffer concentrations were 50mM HEPES, 100mM NaCl and 0.1% BSA buffer, pH 7.4 and optimized to 30 min incubation time. Assay plates were read at 570 nM on a Synergy H4 Plate Reader (Biotek). IC_{50} values were determined from a dose response curve.

[0195] 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 3: Inhibition of Tetra-acetylated Histone H4 Binding to Brd4 bromodomain 1 (BRD4(1)) and Brd 4 bromodomain 2 (BRD4(2))

Example Number	Alpha Screen BRD4(1)	Alpha Screen BRD4(2)	Example Number	Alpha Screen BRD4(1)	Alpha Screen BRD4(2)	Example Number	Alpha Screen BRD4(1)	Alpha Screen BRD4(2)
1	+++	+	2	+	+	3	+	+
4	+	Not Active	5	Not Active	Not Active	6	++	+
7	+++	Not Active	8	+++	Not Active	9	++	Not Active

10	+	++	**11**	+	Not Active	**12**	+	++
13	++	++	**14**	+++	+++	**15**	++	+
16	+++	++	**17**	Not Active	Not Active	**18**	++	+
19	++	+	**20**	++	+	**21**	+	Not Active
22	+	+	**23**	+++	+	**24**	+	+
25	++	+	**26**	+	+	**27**	+	Not Active

Example 29: Inhibition of cMYC expression in cancer cell lines

[0196] MV4-11 cells (CRL-9591) were plated at a density of $2.5x10^4$ 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 cMYC to an internal control, prior to determining the fold expression of each sample, relative to the control.

[0197] 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 c-myc Activity in Human AML MV4-11 cells

Example Number	c-myc activity	Example Number	c-myc activity	Example Number	c-myc activity	Example Number	c-myc activity
1	+	**2**	Not Active	**4**	+	**6**	+
7	+	**8**	Not Active	**9**	+	**10**	Not Active
13	+	**14**	+	**18**	Not Active	**19**	+

Example 30: Inhibition of cell proliferation in cancer cell lines

[0198] MV4-11 cells (CRL-9591) were plated at a density of $5x10^4$ cells per well in 96 well flat bottom plates and treated with increasing concentrations of test compound or DMSO (0.1%) in IMDM media containing 10% 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% CO_2 for 72 h before adding 20 μL of the Cell Titer Aqueous One Solution (Promega) to each well and incubated at 37°C, 5% CO_2 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 5: Inhibition of Cell Proliferation in Human AML MV-4-11 cells

Example Number	Cell Proliferation activity	Example Number	Cell Proliferation activity	Example Number	Cell Proliferation activity	Example Number	Cell Proliferation activity
1	+	2	Not Active	4	+	6	+
7	+	8	Not Active	9	+	10	Not Active
13	+	14	+	-	-	-	-

Example 31: Inhibition of hIL-6 mRNA Transcription

[0200] Human leukemic monocyte lymphoma U937 cells (CRL-1593.2) were plated at a density of 3.2×104 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 (phorbol-13-myristate-12-acetate) at 37°C in 5% CO_2 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 ug/mL lipopolysaccharide from Escherichia coli. Triplicate wells were used for each concentration. The cells were incubated at 37°C, 5% CO_2 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 PCR 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 PCR plates were run on a ViiA™7 real time PCR 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.

[0201] 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 6: Inhibition of hIL-6 mRNA Transcription

Example Number	IL-6 activity	Example Number	IL-6 activity	Example Number	IL-6 activity	Example Number	IL-6 activity
1	+	7	+	8	+	9	+
14	+	-	-	-	-	-	-

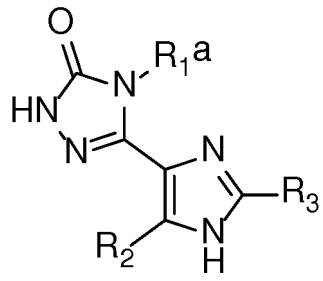
Examples 32: *In vivo* efficacy in athymic nude mouse strain of an acute myeloid leukemia xenograft model using MV4-11 cells

[0202] MV4-11 cells (ATCC) are grown under standard cell culture conditions and (NCr) nu/nu fisol strain of female mice age 6-7 weeks are injected with 5×10^6 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 are randomized based on tumor volume (L x W x H)/2) of average ~100-300 mm^3. Mice are 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, 135 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 are 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 are compared relative to Vehicle control animals. The means, statistical analysis and the comparison between groups are calculated using Student's t-test in Excel.

[0203] 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 of the present disclosure being indicated by the following claims.

Claims

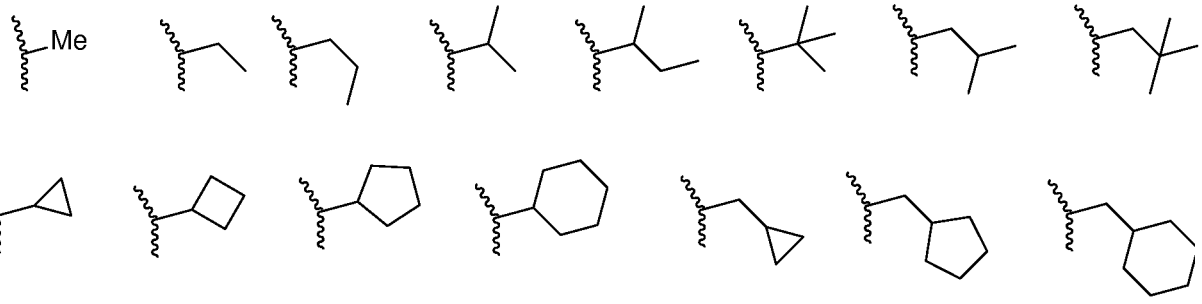
1. A compound of Formula Ia:



Formula Ia

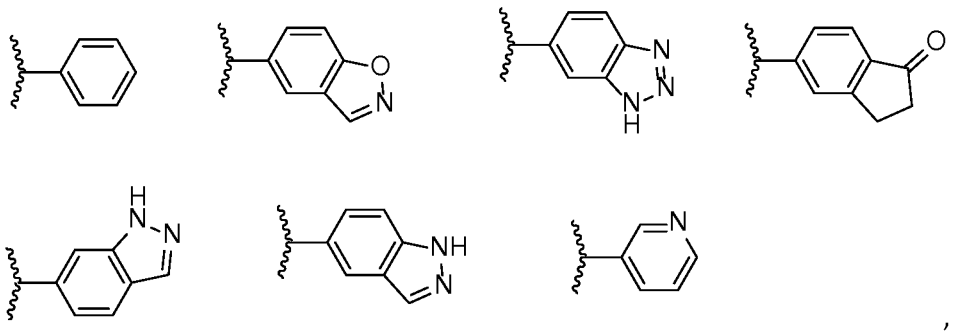
or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

R_{1a} is selected from the following structures:



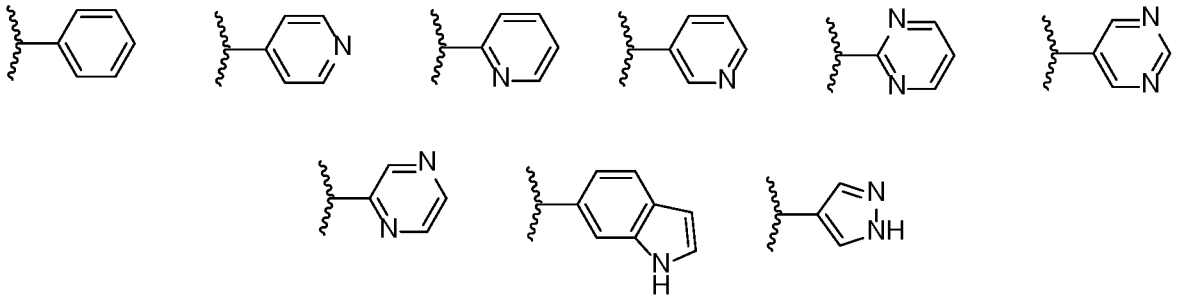
which may be optionally substituted with 1 to 3 groups selected from R_4;
R_2 is

(a) selected from bicyclic aryl and bicyclic heteroaryl groups optionally substituted with 1 to 5 R_5 groups; or
(b) selected from the following structures:



which may be optionally substituted with 1 to 2 groups selected from alkyl (C_1-C_6), halogen, ketone, amide, and ester;

$\mathbf{R_3}$ is selected from the following structures:

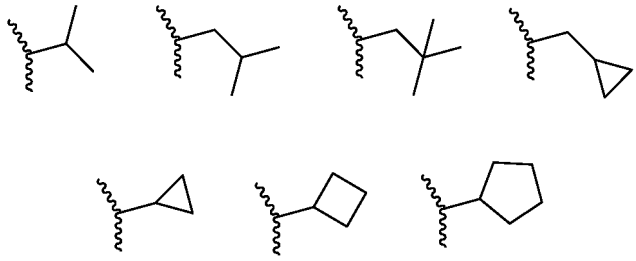


each of which may be optionally substituted with 1 to 5 groups selected from R_5;

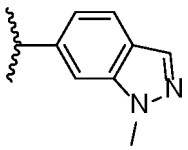
each $\mathbf{R_4}$ is independently selected from deuterium, alkyl (C_1-C_6), cycloalkyl (C_3-C_8), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone, -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thio-alkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo; and

each $\mathbf{R_5}$ is independently selected from deuterium, alkyl (C_1-C_6), alkoxy (C_1-C_6), amino, -NHC(O)NH-alkyl(C_1-C_6), halogen, amide, -CF_3, -CN, -N_3, ketone (C_1-C_6), -S(O)-alkyl(C_1-C_4), -SO_2-alkyl(C_1-C_6), thio-alkyl(C_1-C_6), -COOH, and ester, each of which may be optionally substituted with hydrogen, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, and/or thio-oxo.

2. The compound according to claim 1, wherein R_{1a} is selected from the following structures, which may be optionally substituted with 1 to 3 groups selected from R_4:

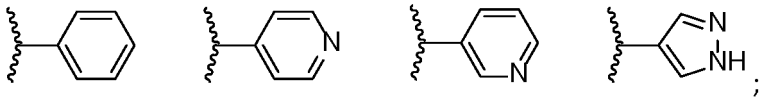


3. The compound according to any one of claims 1-2, wherein R_2 is



4. The compound according to any one of claims 1-3, wherein R_3 is

(a) selected from the following structures, which may be optionally substituted with 1 to 5 groups selected from R_5:



or
(b) an unsubstituted phenyl group.

5. The compound according to claim 1, wherein

(a) the compound is selected from:

3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
Methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methylbenzoate;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methylbenzamide;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)benzamide;
4-Cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
3-(5-(3-Acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one;
3-(5-(5-acetylpyridin-3-yl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one formate;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one;
4-(Cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one;
4-(*tert*-Butyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one;
4-Cyclopentyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclohexyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Isobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(5-(1-Methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-4-neopentyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(3-methylbenzo[*d*]isoxazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(3-methyl-1*H*-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-3-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
3-(2-(1*H*-Indol-6-yl)-5-(1-methyl-1*H*-indazol-6-yl)-1*H*-imidazol-4-yl)-4-cyclopropyl-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1*H*-pyrazol-4-yl)-1H-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;

and stereoisomers, tautomers, pharmaceutically acceptable salts, and hydrates thereof; or

(b) the compound is selected from:

3-(5-(3-acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
methyl 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methyl benzoate hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methyl benzamide hydrochloride;
3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl) benzamide hydrochloride;
4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(3-acetyl-4-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
3-(5-(3-acetyl-5-fluorophenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one hydrochloride;
3-(5-(5-acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one hydrochloride;
4-cyclopropyl-3-(5-(3-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one dihydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;
4-cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;

and stereoisomers, tautomers, and hydrates thereof.

6. A compound selected from:

4-Cyclopropyl-1-methyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-ethyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one;
4-Cyclopropyl-1-(2-methoxyethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one; and
4-cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one hydrochloride;

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

7. A pharmaceutical composition comprising the compound of any one of claims 1-6, and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1-6 for use in therapy.

9. A compound according to any one of claims 1-6 or a composition according to claim 7 for use in method of treating
an autoimmune disease or disorder;
an inflammatory disease or disorder;
an acute non-autoimmune inflammatory disorder **characterized by** disregulation of IL-6 and/or IL-17;
a chronic non-autoimmune inflammatory disorder **characterized by** disregulation of IL-6 and/or IL-17; or
cancer.

10. The compound or composition for use according to claim 9, wherein
the autoimmune or inflammatory disorder is selected from Acute Disseminated Encephalomyelitis, Agammaglobulinemia, Allergic Disease, Ankylosing spondylitis, Anti-GBM/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, Eosinophlic 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, idiopathic pulmonary fibrosis, IgA nephropathy, Inclusion body myositis, Type I diabetes, Interstitial cystitis, Kawasaki's Disease, Leukocytoclastic vasculitis, Lichen planus, Lupus (SLE), Microscopic polyangitis, 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;
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; or
the cancer is selected from Burkitt's lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, bladder cancer, breast cancer, colon carcinoma, colorectal cancer, melanoma, ovarian cancer, prostate cancer, small cell lung carcinoma, non-small cell lung cancer, NUT midline carcinoma, B-cell lymphoma, squamous cell carcinoma and head and neck cancer.

11. The compound or composition for use according to claim 9, wherein the cancer is selected from
a cancer associated with overexpression, translocation, amplification, or rearrangement of a myc family oncoprotein;
a cancer associated with overexpression, translocation, amplification, or rearrangement of BET proteins;
a cancer that relies on pTEFb (Cdk9/cyclin T) and BET proteins to regulate oncogenes;
a cancer associated with upregulation of BET responsive genes CDK6, Bcl2, TYRO3, MYB, and hTERT;
a cancer associated with a gene regulated by a super enhancer;
a cancer that is sensitive to effects of BET inhibition;.
a cancer that is resistant to treatment with immunotherapy, hormone-deprivation therapy, and/or chemotherapy; or
a cancer associated with a virus.

12. The compound or composition for use according to claim 11, wherein
the cancer associated with overexpression, translocation, amplification, or rearrangement of a myc family oncoprotein 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;
the cancer associated with overexpression, translocation, amplification, or rearrangement of BET proteins is selected from NUT midline carcinoma, B-cell lymphoma, non-small cell lung cancer, esophageal cancer, head and neck squamous cell carcinoma, breast cancer, prostate cancer, and colon cancer;
the cancer that relies on pTEFb (Cdk9/cyclin T) and BET proteins to regulate oncogenes 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, and activated, anaplastic large cell lymphoma, neuroblastoma and primary neuroectodermal tumor, rhabdomyosarcoma, prostate cancer, and breast cancer;
the cancer associated with upregulation of BET responsive genes CDK6, Bcl2, TYRO3, MYB, and hTERT 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;
the gene regulated by a superenhancer is the MYC oncogene;
the cancer sensitive to effects of BET inhibition 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), breast cancer, prostate cancer, and colon carcinoma; or
the cancer associated with a virus is associated with a virus 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).

13. A compound or composition for use according to claim 11 wherein the cancer is resistant to treatment with immunotherapy, hormone-deprivation therapy, and/or chemotherapy.

14. The compound or composition for use according to any one of claims 9-13, wherein the method comprises administering said compound or pharmaceutical composition in combination with other therapies, chemotherapeutic agents or antiproliferative agents.

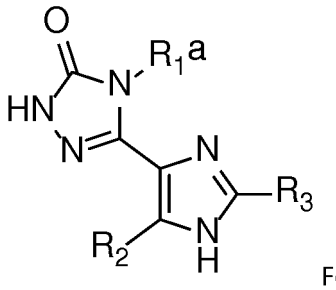
15. A compound of any one of claims 1-6 or a composition according to claim 7, for use in a method of treating a benign proliferative or fibrotic disorder, selected from benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple 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.

16. A compound of any one of claims 1-6 or a composition according to claim 7, for use in a method of treating cardiovascular disease, dyslipidemia, atheroschlerosis, hypercholesterolemia, metabolic syndeome, or Alzheimer's disease;
a metabolic disease or disorder; or
a neurological disease or disorder selected from Alzheimer's disease, Parkinson's disease, Huntington disease, bipolar disorder, schizophrenia, Rubinstein-Taybi syndrome, and epilepsy.

17. The compound or composition for use according to claim 16, wherein the metabolic disorder is selected from obesity-associated inflammation, type II diabetes, and insulin resistance.

Patentansprüche

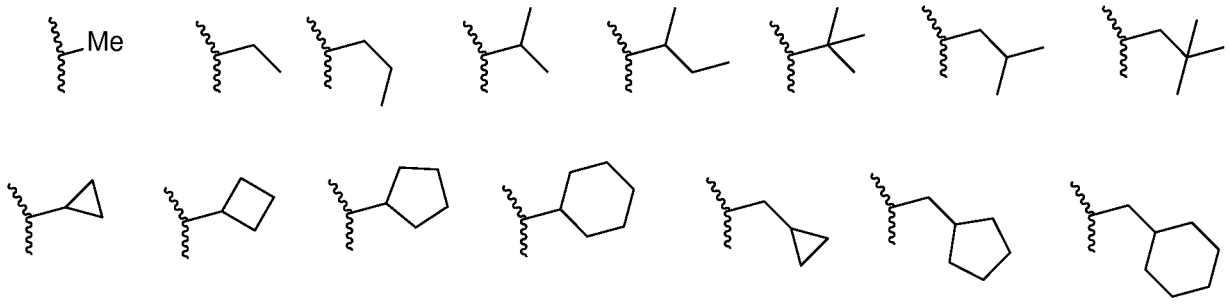
1. Verbindung der Formel Ia:



Formel Ia

oder ein Stereoisomer, Tautomer, pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

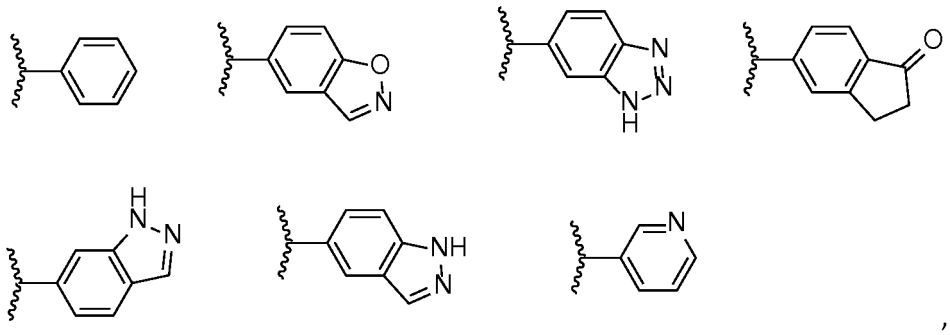
R_{1a} aus den folgenden Strukturen ausgewählt ist:



die gegebenenfalls mit 1 bis 3 Gruppen, ausgewählt aus R_4, substituiert sein können;

R_2

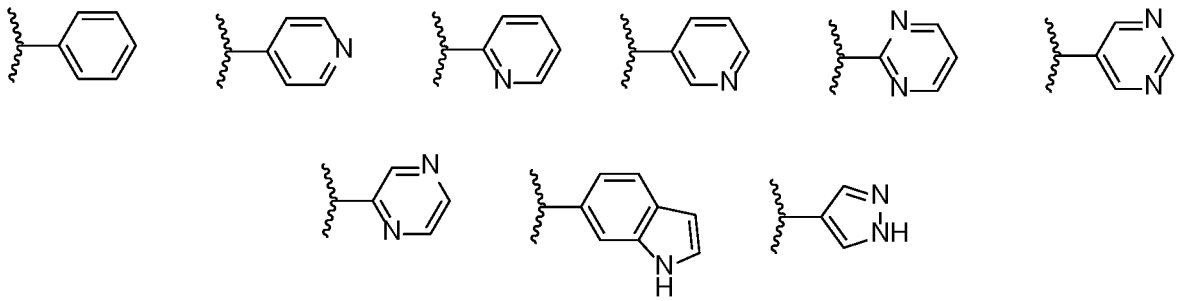
(a) aus bicyclischen Aryl- und bicyclischen Heteroarylgruppen, gegebenenfalls substituiert mit 1 bis 5 R_5-Gruppen, ausgewählt ist; oder
(b) aus den folgenden Strukturen ausgewählt ist:



,

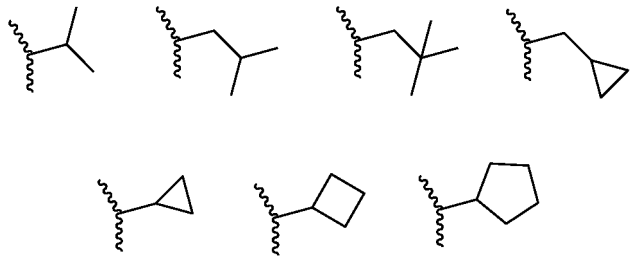
die gegebenenfalls mit 1 bis 2 Gruppen substituiert sein können, ausgewählt aus Alkyl (C_1-C_6), Halogen, Keton, Amid und Ester;

R_3 aus den folgenden Strukturen ausgewählt ist:

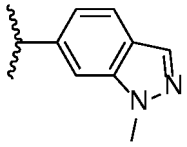


von denen jede gegebenenfalls mit 1 bis 5 Gruppen, ausgewählt aus R_5, substituiert sein kann;
jedes **R_4** unabhängig ausgewählt ist aus Deuterium, Alkyl (C_1-C_6), Cycloalkyl (C_3-C_8), Alkoxy (C_1-C_6), Amino, -NHC(O)NH-Akyl(C_1-C_6), Halogen, Amid, -CF_3, -CN, -N_3, Keton, -S(O)-Akyl(C_1-C_4), -SO_2-Alkyl(C_1-C_6), Thioalkyl(C_1-C_6), -COOH, und Ester, wobei jedes von denen gegebenenfalls mit Wasserstoff, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, Oxo und/oder Thiooxo substituiert sein kann; und
jedes **R_5** unabhängig ausgewählt ist aus Deuterium, Alkyl (C_1-C_6), Alkoxy (C_1-C_6), Amino, -NHC(O)NH-Alkyl(C_1-C_6), Halogen, Amid, -CF_3, -CN, -N_3, Keton (C_1-C_6), -S(O)-Alkyl(C_1-C_4), -SO_2-Alkyl(C_1-C_6), Thioalkyl(C_1-C_6), -COOH und Ester, wobei jedes von denen gegebenenfalls mit Wasserstoff, F, Cl, Br, -OH, -NH_2, -NHMe, -OMe, -SMe, Oxo und/oder Thiooxo substituiert sein kann.

2. Verbindung nach Anspruch 1, wobei R_{1a} aus den folgenden Strukturen ausgewählt ist, die gegebenenfalls mit 1 bis 3 Gruppen, ausgewählt aus R_4, substituiert sein können:



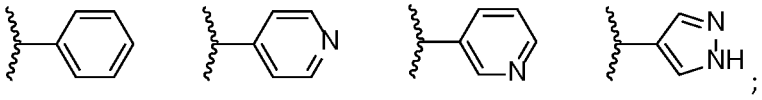
3. Verbindung nach einem der Ansprüche 1 bis 2, wobei R_2



ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R_3

(a) aus den folgenden Strukturen ausgewählt ist, die gegebenenfalls mit 1 bis 5 Gruppen, ausgewählt aus R_5, substituiert sein können:



oder
(b) eine unsubstituierte Phenylgruppe ist.

5. Verbindung nach Anspruch 1, wobei

(a) die Verbindung ausgewählt ist aus:

3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on;
Methyl-3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methylbenzoat;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methylbenzamid;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)benzamid;
4-Cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on;
4-Cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on;
3-(5-(3-Acetyl-4-fluorphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on;
3-(5-(3-Acetyl-5-fluorphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-on;
3-(5-(5-Acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-on;
3-(5-(5-Acetylpyridin-3-yl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on-formiat;
4-Cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on;
4-(Cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Isopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-on;
4-(*tert*-Butyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-on;
4-Cyclopentyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;

4-Cyclobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclohexyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Isobutyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
3-(5-(1-Methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-4-neopentyl-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(3-methylbenzo[*d*]isoxazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(3-methyl-1*H*-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(pyridin-3-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
3-(2-(1*H*-Indol-6-yl)-5-(1-methyl-1*H*-indazol-6-yl)-1*H*-imidazol-4-yl)-4-cyclopropyl-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1*H*-pyrazol-4-yl)-1H-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;

und Stereoisomeren, Tautomeren, pharmazeutisch verträglichen Salzen und Hydraten davon; oder
(b) die Verbindung ausgewählt ist aus:

3-(5-(3-Acetylphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
Methyl-3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-4-methylbenzoat-Hydrochlorid;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-N-methylbenzamid-Hydrochlorid;
3-(4-(4-Cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenyl-1H-imidazol-5-yl)-benzamid-Hydrochlorid;
4-Cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-inden-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(2-phenyl-5-(3-propionylphenyl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
3-(5-(3-Acetyl-4-fluorphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
3-(5-(3-Acetyl-5-fluorphenyl)-2-phenyl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-5-yl)-2-phenyl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-on-Hydrochlorid;
3-(5-(5-Acetyl-2-methylphenyl)-2-phenyl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(3-methyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1,3-dimethyl-1H-indazol-5-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Dihydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Dihydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;
4-Cyclopropyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;

und Stereoisomeren, Tautomeren und Hydraten davon.

6. Verbindung, ausgewählt aus:

4-Cyclopropyl-1-methyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-1-ethyl-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-1-(cyclopropylmethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on;
4-Cyclopropyl-1-(2-methoxyethyl)-3-(5-(1-methyl-1*H*-indazol-6-yl)-2-phenyl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-on; und
4-Cyclopropyl-1-methyl-3-(5-(1-methyl-1H-indazol-6-yl)-2-phenyl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-on-Hydrochlorid;

oder einem Stereoisomer, Tautomer, pharmazeutisch verträglichen Salz oder Hydrat von irgendeinem davon.

7. Pharmazeutische Zusammensetzung, umfassend die Verbindung nach einem der Ansprüche 1 bis 6, und einen pharmazeutisch verträglichen Träger.

8. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung in der Therapie.

9. Verbindung nach einem der Ansprüche 1 bis 6 oder eine Zusammensetzung nach Anspruch 7 zur Verwendung im Verfahren zur Behandlung
einer Autoimmunerkrankung oder -störung;
einer Entzündungserkrankung oder -störung;
einer akuten nicht-autoimmunen Entzündungsstörung, **gekennzeichnet durch** eine Dysregulation von IL-6 und/oder IL-17;
einer chronischen nicht-autoimmunen Entzündungsstörung, **gekennzeichnet durch** eine Dysregulation von IL-6 und/oder IL-7; oder
von Krebs.

10. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 9, wobei
die Autoimmun- oder Entzündungsstörung ausgewählt ist aus der akuten disseminierten Enzephalomyelitis, der Agammaglobulinämie, der allergischen Erkrankung, der ankylosierenden Spondylitis, der Anti-GBM-/Anti-TBM-Nephritis, dem Antiphospholipid-Syndrom, der autoimmun bedingten aplastischen Anämie, der Autoimmunhepatitis, der autoimmunen Innenohrerkrankung, der Autoimmunmyokarditis, der Autoimmunpankreatitis, der Autoimmunretinopathie, der autoimmunthrombozytopenischen Purpura, dem Morbus Behçet, dem bullösen Pemphigoid, dem Morbus Castleman, der Zöliakie, dem Churg-Strauss-Syndrom, dem Morbus Crohn, dem Cogan-Syndrom, dem Trockenen-Auge-Syndrom, der essentiellen gemischten Kryoglobulinämie, der Dermatomyositis, dem Morbus Devic, der Enzephalitis, der eosinophilen Ösophagitis, der eosinophilen Fasziitis, dem Erythema nodosum, der Riesenzell-Arteriitis, der Glomerulonephritis, dem Goodpasture-Syndrom, der Granulomatose mit Polyangiitis (Wegener-Granulomatose), dem Morbus Grave, dem Guillain-Barre-Syndrom, der Hashimoto-Thyreoiditis, der hämolytischen Anämie, der Purpura Schönlein-Henoch, der idiopathischen Lungenfibrose, der IgA-Nephropathie, der Einschlusskörperchen-Myositis, dem Typ-I-Diabetes, der interstitiellen Zystitis, dem Morbus Kawasaki, der leukozytoklastischen Vaskulitis, dem Lichen planus, dem Lupus (SLE), der mikroskopischen Polyangiitis, der multiplen Sklerose, der Myasthenia gravis, der Myositis, der optischen Neuritis, dem Pemphigus, dem POEMS-Syndrom, der Polyarteriitis nodosa, der primär biliären Zirrhose, der Psoriasis, der psoriatischen Arthritis, dem Pyoderma gangraenosum, der rezidivierenden Polychondritis, der rheumatoiden Arthritis, der Sarkoidose, der Sklerodermie, dem Sjögren-Syndrom, der Takayasu-Arteriitis, der transversen Myelitis, der ulzerativen Kolitis, der Uveitis und der Vitiligo;
die akute oder chronische nicht autoimmune Entzündungsstörung ausgewählt ist aus der Sinusitis, der Pneumonitis, der Osteomyelitis, der Gastritis, der Enteritis, der Gingivitis, der Appendizitis, dem Reizdarmsyndrom, der Gewebetransplantatabstoßung, der chronisch obstruktiven Lungenerkrankung (COPD), dem septischem Schock, der Osteoarthritis, der akuten Gicht, der akuten Lungenverletzung, dem akuten Nierenversagen, Verbrennungen, der Herxheimer-Reaktion und dem SIRS (systemischen inflammatorischen Response-Syndrom), assoziiert mit Virusinfektionen; oder
der Krebs ausgewählt ist aus dem Burkitt-Lymphom, dem Hodgkin-Lymphom, dem Non-Hodgkin-Lymphom, dem diffusen großzelligen B-Zell-Lymphom, dem follikulären Lymphom, dem multiplen Myelom, dem Blasenkrebs, dem Brustkrebs, dem Kolonkarzinom, dem kolorektalen Krebs, dem Melanom, dem Ovarialkrebs, dem Prostatakrebs,

dem kleinzelligen Lungenkarzinom, dem nicht-kleinzelligen Lungenkrebs, dem NUT-Mittellinienkarzinom, dem B-Zell-Lymphom, dem Plattenepithelkarzinom und dem Kopf- und Halskrebs.

11. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 9, wobei der Krebs ausgewählt ist aus einem Krebs, assoziiert mit einer Überexpression, Translokation, Amplifikation oder einem Rearrangement eines Onkoproteins aus der myc-Familie;
einem Krebs, assoziiert mit einer Überexpression, Translokation, Amplifikation oder einem Rearrangement von BET-Proteinen;
einem Krebs, der zur Regulation der Onkogene auf pTEFb (Cdk9/Cyclin T)- und BET-Proteine angewiesen ist;
einem Krebs, assoziiert mit der Hochregulation von BET-responsiven Genen CDK6, Bcl2, TYRO3, MYB und hTERT;
einem Krebs, assoziiert mit einem durch einen Super-Enhancer regulierten Gen;
einem Krebs, der gegenüber Wirkungen der BET-Inhibition empfindlich ist;
einem Krebs, der gegenüber einer Immuntherapie, Hormon-Deprivationstherapie und/oder einer Chemotherapie behandlungsresistent ist; oder
einem Krebs, assoziiert mit einem Virus.

12. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 11, wobei
der Krebs, assoziiert mit einer Überexpression, Translokation, Amplifikation oder einem Rearrangement eines Onkoproteins aus der myc-Familie, ausgewählt ist aus der akuten B-Lymphozytenleukämie, dem Burkitt-Lymphom, dem diffusen großzelligen Lymphom, dem multiplen Myelom, der primären Plasmazellleukämie, dem atypischen Karzinoid beim Lungenkrebs, dem Blasenkrebs, dem Brustkrebs, dem Zervixkrebs, dem Kolonkrebs, dem Magenkrebs, dem Glioblastom, dem hepatozellulären Karzinom, dem großzelligen neuroendokrinen Karzinom, dem Medulloblastom, dem Melanom, dem nodulären Melanom, dem superfiziell spreitenden Neuroblastom, dem Ösophagus-Plattenepithelkarzinom, dem Osteosarkom, dem Ovarialkrebs, dem Prostatakrebs, dem klaren Nierenzellkarzinom, dem Retinoblastom, dem Rhabdomyosarkom und dem kleinzelligen Lungenkarzinom;
der Krebs, assoziiert mit einer Überexpression, Translokation, Amplifikation oder dem Rearrangement von BET-Proteinen, ausgewählt ist aus dem NUT-Mittellinienkarzinom, dem B-Zelllymphom, dem nicht-kleinzelligen Lungenkrebs, dem Ösophaguskrebs, dem Kopf- und Hals-Plattenepithelkarzinom, dem Brustkrebs, dem Prostatakrebs und dem Kolonkrebs;
der Krebs, der zur Regulation von Onkogenen auf pTEFb(Cdk9/Cyclin T)- und BET-Proteine angewiesen ist, ausgewählt ist aus der chronischen lymphatischen Leukämie und dem multiplen Myelom, dem follikulären Lymphom, dem diffusen großzelligen B-Zell-Lymphom mit Keimzentrum-Phänotyp, dem Burkitt-Lymphom, dem Hodgkin-Lymphom und dem aktivierten anaplastischen Großzelllymphom, dem Neuroblastom und dem primären neuroektodermalen Tumor, dem Rhabdomyosarkom, dem Prostatakrebs und dem Brustkrebs;
der Krebs, assoziiert mit der Hochregulation von BET-responsiven Genen CDK6, Bcl2, TYRO3, MYB und hTERT, ausgewählt ist aus dem Pankreaskrebs, dem Brustkrebs, dem Kolonkrebs, dem Glioblastom, dem adenoid-zystischen Karzinom, der T-Zell-Prolymphozytenleukämie, dem malignen Gliom, dem Blasenkrebs, dem Medulloblastom, dem Schilddrüsenkrebs, dem Melanom, dem multiplen Myelom, dem Barret-Adenokarzinom, dem Hepatom, dem Prostatakrebs, der Promyelozytenleukämie, der chronischen lymphatischen Leukämie, dem Mantelzell-Lymphom, dem diffusen großzelligen B-Zelllymphom, dem kleinzelligen Lungenkrebs und dem Nierenzellkarzinom;
das durch einen Super-Enhancer regulierte Gen das MYC-Onkogen ist;
der Krebs, empfindlich gegenüber Wirkungen der BET-Inhibition, ausgewählt ist aus dem NUT-Mittellinienkarzinom (NMV), der akuten myeloischen Leukämie (AML), der akuten B-lymphoblastischen Leukämie (B-ALL), dem Burkitt-Lymphom, dem B-Zelllymphom, dem Melanom, der gemischtlinigen Leukämie, dem multiplen Myelom, der Promyelozytenleukämie (PML), dem Non-Hodgkin-Lymphom, dem Neuroblastom, dem Medulloblastom, dem Lungenkarzinom (NSCLC, SCLC), dem Brustkrebs, dem Prostatakrebs und dem Kolonkarzinom; oder
der mit einem Virus assoziierte Krebs assoziiert ist mit einem Virus, ausgewählt aus dem Epstein-Barr-Virus (EBV), dem Hepatitis-B-Virus (HBV), dem Hepatitis-C-Virus (HCV), dem Kaposi-Sarkom-assoziierten Virus (KSHV), dem humanen Papillomavirus (HPV), dem Merkel-Zell-Polyomavirus und dem humanen Zytomegalovirus (CMV).

13. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 11, wobei der Krebs gegenüber einer Immuntherapie, einer Hormon-Deprivationstherapie und/oder einer Chemotherapie behandlungsresistent ist.

14. Verbindung oder Zusammensetzung zur Verwendung nach einem der Ansprüche 9 bis 13, wobei das Verfahren die Verabreichung der genannten Verbindung oder pharmazeutischen Zusammensetzung in Kombination mit anderen Therapien, chemotherapeutischen Mitteln oder antiproliferativen Mitteln umfasst.

15. Verbindung nach einem der Ansprüche 1 bis 6 oder eine Zusammensetzung nach Anspruch 7, zur Verwendung in

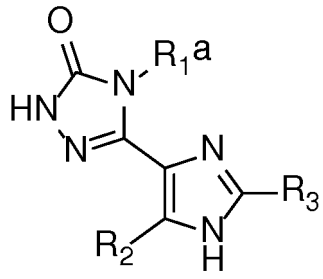
einem Verfahren zur Behandlung einer benignen proliferativen oder fibrotischen Störung, ausgewählt aus benignen Weichteiltumoren, Knochentumoren, Hirn- und Spinaltumoren, Augenlid- und Orbitaltumoren, einem Granulom, einem Lipom, einem Meningiom, einer multiplen endokrinen Neoplasie, Nasenpolypen, Hypophysentumoren, einem Prolaktinom, einem zerebralen Pseudotumor, seborrhoischen Keratosen, Magenpolypen, Schilddrüsenknötchen, zystischen Neoplasmen des Pankreas, Hämangiomen, Stimmbandknötchen, Polypen und Zysten, dem Morbus Castleman, der chronischen Sinus pilonidalis-Erkrankung, dem Dermatofibrom, der Pilarzyste, dem pyogenen Granulom, dem juvenilen Polyposis-Syndrom, der idiopathischen Lungenfibrose, der Nierenfibrose, der postoperativen Striktur, der Keloidbildung, der Sklerodermie und der Herzfibrose.

16. Verbindung nach einem der Ansprüche 1 bis 6 oder eine Zusammensetzung nach Anspruch 7, zur Verwendung in einem Verfahren zur Behandlung von
einer kardiovaskulären Erkrankung, der Dyslipidämie, der Atherosklerose, der Hypercholesterinämie, dem metabolischen Syndrom oder dem Morbus Alzheimer;
einer metabolischen Erkrankung oder Störung; oder
einer neurologischen Erkrankung oder Störung, ausgewählt aus dem Morbus Alzheimer, dem Morbus Parkinson, dem Morbus Huntington, der Bipolar Störung, der Schizophrenie, dem Rubinstein-Taybi-Syndrom und der Epilepsie.

17. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 16, wobei die metabolische Störung aus der Adipositas-assoziierten Entzündung, dem Typ-II-Diabetes und der Insulinresistenz ausgewählt ist.

Revendications

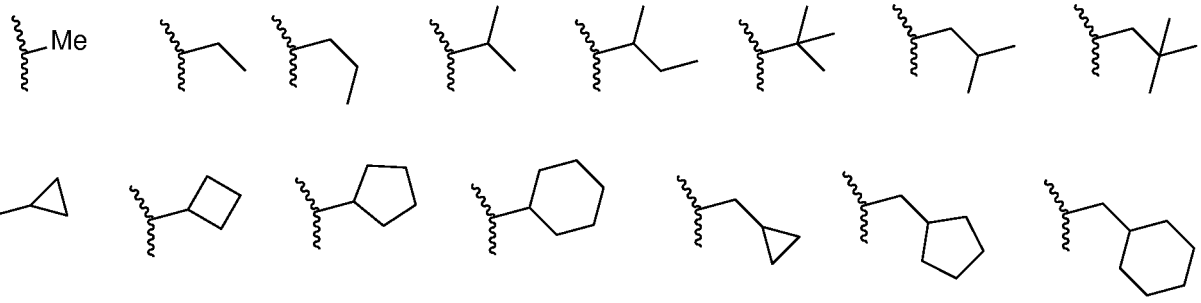
1. Composé ayant la formule Ia :



Formule Ia

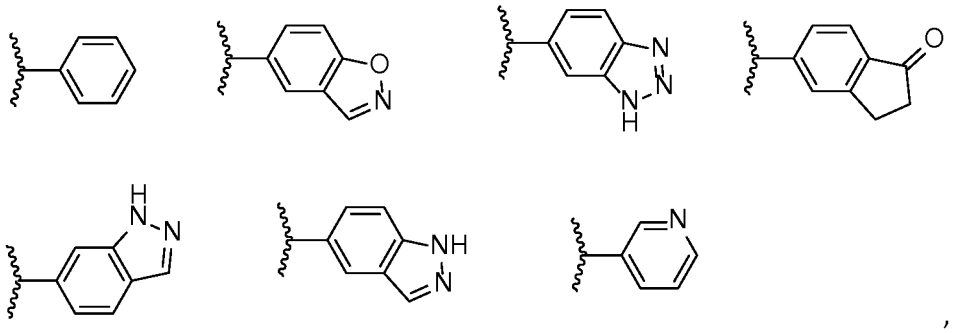
ou stéréoisomère, tautomère, sel pharmaceutiquement acceptable, ou hydrate de celui-ci,
dans lequel :

R_{1a} est sélectionné parmi les structures suivantes :



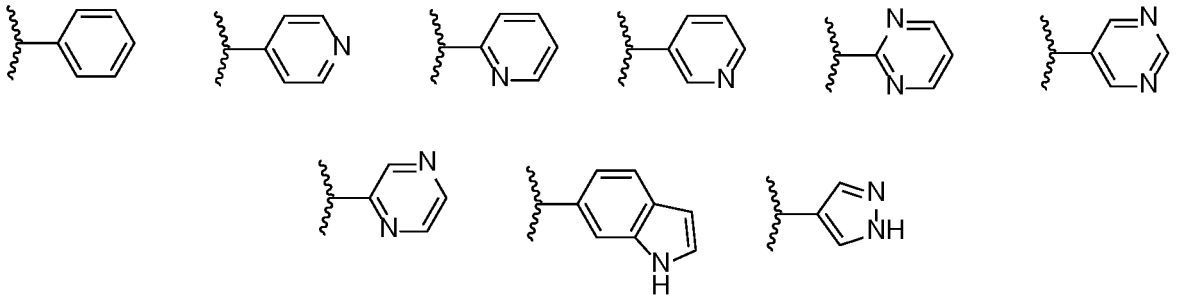
qui peuvent être optionnellement substituées avec 1 à 3 groupes sélectionnés parmi des groupes R_4;
R_2 est

(a) sélectionné parmi des groupes aryle bicycliques et hétéroaryle bicycliques, optionnellement substitués avec 1 à 5 groupes R_5 ; ou
(b) sélectionné parmi les structures suivantes :



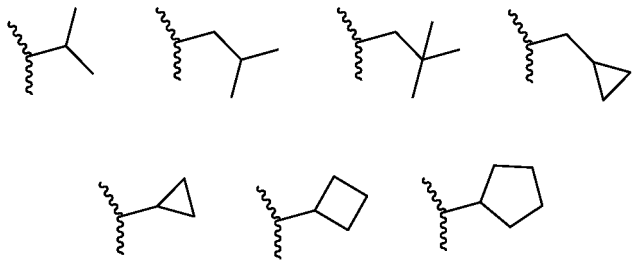
qui peuvent être optionnellement substituées avec 1 à 2 groupes sélectionnés parmi des groupes alkyle C_1-C_6, halogène, cétone, amide, et ester ;

R_3 est sélectionné parmi les structures suivantes :

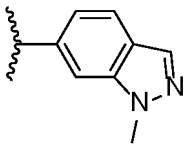


dont chacune peut être optionnellement substituée avec 1 à 5 groupes sélectionnés parmi des groupes R_5 ; chaque groupe **R_4** est sélectionné indépendamment parmi le deutérium et des groupes alkyle C_1-C_6, cycloalkyle C_3-C_8, alcoxy C_1-C_6, amino, -NHC(O)NH-alkyle C_1-C_6, halogène, amide, -CF_3, -CN, -N_3, cétone, -S(O)-alkyle C_1-C_4, -SO_2-alkyle C_1-C_6, thioalkyle C_1-C_6, -COOH, et ester, dont chacun peut être optionnellement substitué avec un atome d'hydrogène, F, Cl, Br, ou un groupe -OH, -NH_2, -NHMe, -OMe, -SMe, oxo, et/ou thio-oxo ; et chaque groupe **R_5** est sélectionné indépendamment parmi le deutérium et des groupes alkyle C_1-C_6, alcoxy C_1-C_6, amino, -NHC(O)NH-alkyle C_1-C_6, halogène, amide, -CF_3, -CN, -N_3, cétone C_1-C_6, - S(O)-alkyle C_1-C_4, -SO_2-alkyle C_1-C_6, thioalkyle C_1-C_6, -COOH, et ester, dont chacun peut être optionnellement substitué avec un atome d'hydrogène, F, Cl, Br, ou un groupe -OH, -NH_2, - NHMe, -OMe, -SMe, oxo, et/ou thio-oxo.

2. Composé selon la revendication 1, dans lequel R_{1a} est sélectionné parmi les structures suivantes, qui peuvent être optionnellement substituées avec 1 à 3 groupes sélectionnés parmi des groupes R_4 :

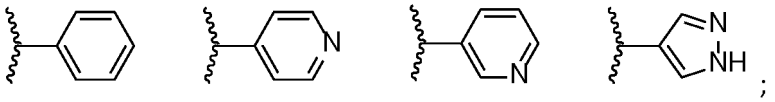


3. Composé selon l'une quelconque des revendications 1 ou 2, dans lequel R_2 est



4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel R_3 est

(a) sélectionné parmi les structures suivantes, qui peuvent être optionnellement substituées avec 1 à 5 groupes sélectionnés parmi des groupes R_5 :



;

ou

(b) un groupe phényle non substitué.

5. Composé selon la revendication 1, dans lequel :

(a) le composé est sélectionné parmi :

la 3-(5-(3-acétylphényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
le 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)-4-méthylbenzoate de méthyle ;
le 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)-N-méthylbenzamide ;
le 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)benzamide ;
la 4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-indén-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
la 4-cyclopropyl-3-(2-phényl-5-(3-propionylphényl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
la 3-(5-(3-acétyl-4-fluorophényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
la 3-(5-(3-acétyl-5-fluorophényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-5-yl)-2-phényl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one ;
la 3-(5-(5-acétyl-2-méthylphényl)-2-phényl-1*H*-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one ;
le formiate de 3-(5-(5-acétylpyridin-3-yl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
la 4-cyclopropyl-3-(5-(1,3-diméthyl-1H-indazol-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
la 4-(cyclopropylméthyl)-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-isopropyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one ;
la 4-(*tert*-Butyl)-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopentyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclobutyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclohexyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-isobutyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-4-néopentyl-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(3-méthylbenzo[*d*]isoxazol-5-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(3-méthyl-1*H*-indazol-5-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-(pyridin-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-(pyridin-3-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 3-(2-(1*H*-Indol-6-yl)-5-(1-méthyl-1*H*-indazol-6-yl)-1*H*-imidazol-4-yl)-4-cyclopropyl-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-(1*H*-pyrazol-4-yl)-1H-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-(1-méthyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-4-yl)-1*H*-1,2,4-

triazol-5(4*H*)-one ;

et des stéréoisomères, tautomères, sels pharmaceutiquement acceptables, et hydrates de ceux-ci ; ou
(b) le composé est sélectionné parmi :

l'hydrochlorure de 3-(5-(3-acétylphényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)-4-méthylbenzoate de méthyle ;
l'hydrochlorure de 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)-N-méthylbenzamide ;
l'hydrochlorure de 3-(4-(4-cyclopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phényl-1H-imidazol-5-yl)benzamide ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(3-oxo-2,3-dihydro-1H-indén-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(2-phényl-5-(3-propionylphényl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 3-(5-(3-acétyl-4-fluorophényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 3-(5-(3-acétyl-5-fluorophényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one ;
l'hydrochlorure de 3-(5-(5-acétyl-2-méthylphényl)-2-phényl-1H-imidazol-4-yl)-4-cyclopropyl-1H-1,2,4-triazol-5(4*H*)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(3-méthyl-1H-indazol-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorurede4-cyclopropyl-3-(5-(1-méthyl-1H-benzo[d][1,2,3]triazo1-6-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(1,3-diméthyl-1H-indazol-5-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
le dihydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
le dihydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-(pyridin-3-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-(1-méthyl-1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;
l'hydrochlorure de 4-cyclopropyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-(1H-pyrazol-4-yl)-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;

et des stéréoisomères, tautomères, et hydrates de ceux-ci.

6. Composé sélectionné parmi :

la 4-cyclopropyl-1-méthyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-1-éthyl-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-1-(cyclopropylméthyl)-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ;
la 4-cyclopropyl-1-(2-méthoxyéthyl)-3-(5-(1-méthyl-1*H*-indazol-6-yl)-2-phényl-1*H*-imidazol-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-one ; et
l'hydrochlorure de 4-cyclopropyl-1-méthyl-3-(5-(1-méthyl-1H-indazol-6-yl)-2-phényl-1H-imidazol-4-yl)-1H-1,2,4-triazol-5(4H)-one ;

ou un stéréoisomère, tautomère, sel pharmaceutiquement acceptable, ou hydrate de l'un quelconque de ceux-ci.

7. Composition pharmaceutique comprenant le composé selon l'une quelconque des revendications 1 à 6, et un support pharmaceutiquement acceptable.

8. Composé selon l'une quelconque des revendications 1 à 6, destiné à un usage thérapeutique.

9. Composé selon l'une quelconque des revendications 1 à 6 ou composition selon la revendication 7, destiné(e) à une utilisation dans une méthode de traitement
d'une maladie ou d'une affection auto-immune ;
d'une maladie ou d'une affection inflammatoire ;
d'une affection inflammatoire aiguë non auto-immune **caractérisée par** une dérégulation de l'IL-6 et/ou de l'IL-17 ;
d'une affection inflammatoire chronique non auto-immune **caractérisée par** une dérégulation de l'IL-6 et/ou de l'IL-17 ; ou
d'un cancer.

10. Composé ou composition destiné(e) à une utilisation selon la revendication 9, dans lequel ou dans laquelle :

l'affection auto-immune ou inflammatoire est sélectionnée parmi une encéphalomyélite aiguë disséminée, une agammaglobulinémie, une maladie allergique, une spondylarthrite ankylosante, une néphrite anti-GBM/anti-TBM, un syndrome antiphospholipides, une anémie aplasique auto-immune, une hépatite auto-immune, une pathologie labyrinthique auto-immune, une myocardite auto-immune, une pancréatite auto-immune, une rétinopathie auto-immune, un purpura thrombocytopénique auto-immun, la maladie de Behçet, une pemphigoïde bulleuse, la maladie de Castleman, la maladie coeliaque, le syndrome de Churg-Strauss, la maladie de Crohn, le syndrome de Cogan, le syndrome des yeux secs, une cryoglobulinémie mixte essentielle, une dermatomyosite, la maladie de Devic, une encéphalite, une oesophagite à éosinophiles, une fasciite à éosinophiles, un érythème noueux, une artérite à cellules géantes, une glomérulonéphrite, un syndrome de Goodpasture, une granulomatose avec polyangéite (de Wegener), la maladie de Graves, le syndrome de Guillain-Barré, la thyroïdite d'Hashimoto, une anémie hémolytique, le purpura de Schönlein-Henoch, une fibrose pulmonaire idiopathique, une néphropathie IgA, une myosite à corps d'inclusions, un diabète de type I, une cystite interstitielle, la maladie de Kawasaki, une vascularite leucocytoclasique, un lichen plan, un lupus (LED), une polyangite microscopique, une sclérose en plaques, une myasthénie grave, une myosite, une névrite optique, un pemphigus, le syndrome POEMS, une polyartérite noueuse, une cirrhose biliaire primitive, un psoriasis, une arthrite psoriasique, une pyodermie phadégénique, une polychondrite récidivante, une polyarthrite rhumatoïde, une sarcoïdose, une sclérodermie, le syndrome de Sjögren, l'artérite de Takayasu, une myélite transverse, une colite ulcéreuse, une uvéite et un vitiligo ;
l'affection inflammatoire aiguë ou chronique non auto-immune est sélectionnée parmi une sinusite, une pneumonite, une ostéomyélite, une gastrite, une entérite, une gingivite, une appendicite, un syndrome du côlon irritable, un rejet de greffe tissulaire, une bronchopneumopathie chronique obstructive (BPCO), un choc septique, une arthrose, une goutte aiguë, une lésion pulmonaire aiguë, une insuffisance rénale aiguë, des brûlures, une réaction d'Herxheimer et un syndrome de réponse inflammatoire systémique (SRIS) associé à des infections virales ; ou
le cancer est sélectionné parmi un lymphome de Burkitt, un lymphome de Hodgkin, un lymphome non hodgkinien, un lymphome diffus à grandes cellules B, un lymphome folliculaire, un myélome multiple, un cancer de la vessie, un cancer du sein, un carcinome du côlon, un cancer colorectal, un mélanome, un cancer de l'ovaire, un cancer de la prostate, un carcinome pulmonaire à petites cellules, un cancer du poumon non à petites cellules, un carcinome de la ligne médiane NUT, un lymphome à cellules B, un carcinome épidermoïde, et un cancer des voies aérodigestives supérieures.

11. Composé ou composition destiné(e) à une utilisation selon la revendication 9, le cancer étant sélectionné parmi :

un cancer associé à une surexpression, une translocation, une amplification, ou un réarrangement d'une oncoprotéine de la famille myc ;
un cancer associé à une surexpression, une translocation, une amplification, ou un réarrangement de protéines BET ;
un cancer qui dépend de protéines pTEFb (Cdk9/cycline T) et BET pour réguler les oncogènes ;
un cancer associé à une régulation positive de gènes CDK6, Bcl2, TYRO3, MYB, et hTERT sensibles aux protéines BET ;
un cancer associé à un gène régulé par un superactivateur ;
un cancer qui est sensible aux effets de l'inhibition des protéines BET ;

un cancer qui est résistant à un traitement par immunothérapie, un traitement anti-hormonal, et/ou une chimiothérapie ; ou
un cancer associé à un virus.

12. Composé ou composition destiné(e) à une utilisation selon la revendication 11, dans lequel ou dans laquelle :

le cancer associé à une surexpression, une translocation, une amplification, ou un réarrangement d'une oncoprotéine de la famille myc, est sélectionné parmi une leucémie lymphocytaire aiguë B, un lymphome de Burkitt, un lymphome diffus à grandes cellules, un myélome multiple, une leucémie à plasmocytes primitive, un carcinoïde pulmonaire atypique, un cancer de la vessie, un cancer du sein, un cancer du col de l'utérus, un cancer du côlon, un cancer de l'estomac, un glioblastome, un carcinome hépatocellulaire, un carcinome neuroendocrinien à grandes cellules, un médulloblastome, un mélanome, un mélanome nodulaire à extension superficielle, un neuroblastome, un carcinome épidermoïde oesophagien, un ostéosarcome, un cancer de l'ovaire, un cancer de la prostate, un carcinome rénal à cellules claires, un rétinoblastome, un rhabdomyosarcome et un carcinome pulmonaire à petites cellules ;
le cancer associé à une surexpression, une translocation, une amplification, ou un réarrangement de protéines BET, est sélectionné parmi un carcinome de la ligne médiane NUT, un lymphome à cellules B, un cancer du poumon non à petites cellules, un cancer de l'oesophage, un carcinome épidermoïde des voies aérodigestives supérieures, un cancer du sein, un cancer de la prostate et un cancer du côlon ;
le cancer qui dépend de protéines pTEFb (Cdk9/cycline T) et BET pour réguler les oncogènes est sélectionné parmi une leucémie lymphocytaire chronique et un myélome multiple, un lymphome folliculaire, un lymphome diffus à grandes cellules B avec un phénotype de type centre germinatif, un lymphome de Burkitt, un lymphome de Hodgkin, et un lymphome à grandes cellules anaplasiques activées, un neuroblastome et une tumeur neuroectodermique primitive, un rhabdomyosarcome, un cancer de la prostate et un cancer du sein ;
le cancer associé à une régulation positive de gènes CDK6, Bcl2, TYRO3, MYB, et hTERT sensibles aux protéines BET est sélectionné parmi un cancer du pancréas, un cancer du sein, un cancer du côlon, un glioblastome, un carcinome adénoïde kystique, une leucémie prolymphocytaire à cellules T, un gliome malin, un cancer de la vessie, un médulloblastome, un cancer de la thyroïde, un mélanome, un myélome multiple, un adénocarcinome de Barrett, un hépatome, un cancer de la prostate, une leucémie promyélocytaire, une leucémie lymphocytaire chronique, un lymphome à cellules du manteau, un lymphome diffus à grandes cellules B, un cancer du poumon à petites cellules et un carcinome rénal ;
le gène régulé par un superactivateur est l'oncogène MYC ;
le cancer sensible aux effets de l'inhibition des protéines BET est sélectionné parmi un carcinome de la ligne médiane NUT (NMC), une leucémie myéloïde aiguë (LMA), une leucémie aiguë lymphoblastique à cellules B (LAL-B), un lymphome de Burkitt, un lymphome à cellules B, un mélanome, une leucémie de lignée mixte, un myélome multiple, une leucémie promyélocytaire (LPM), un lymphome non hodgkinien, un neuroblastome, un médulloblastome, un carcinome pulmonaire (CPNPC, CPPC), un cancer du sein, un cancer de la prostate et un carcinome du côlon ; ou
le cancer associé à un virus est associé à un virus sélectionné parmi le virus d'Epstein-Barr (VEB), le virus de l'hépatite B (VHB), le virus de l'hépatite C (VHC), le virus associé au sarcome de Kaposi (KSHV), le virus du papillome humain (VPH), le polyomavirus des cellules de Merkel, et le cytomégalovirus (CMV) humain.

13. Composé ou composition destiné(e) à une utilisation selon la revendication 11, le cancer étant résistant à un traitement par immunothérapie, un traitement anti-hormonal, et/ou une chimiothérapie.

14. Composé ou composition destiné(e) à une utilisation selon l'une quelconque des revendications 9 à 13, le procédé comprenant l'administration dudit composé ou de ladite composition pharmaceutique en combinaison avec d'autres thérapies, agents chimiothérapeutiques ou agents antiprolifératifs.

15. Composé selon l'une quelconque des revendications 1 à 6 ou composition selon la revendication 7, destiné(e) à une utilisation dans une méthode de traitement d'une affection proliférative ou fibrotique bénigne, sélectionnée parmi des tumeurs bénignes des tissus mous, des tumeurs osseuses, des tumeurs cérébrales et spinales, des tumeurs de la paupière et de l'orbite, un granulome, un lipome, un méningiome, une néoplasie endocrinienne multiple, des polypes nasaux, des tumeurs de l'hypophyse, un prolactinome, une pseudotumeur cérébrale, des kératoses séborrhéiques, des polypes de l'estomac, des nodules thyroïdiens, des néoplasmes kystiques du pancréas, des hémangiomes, des nodules, des polypes et des kystes des cordes vocales, la maladie de Castelman, une maladie pilonidale chronique, un dermatofibrome, un kyste pilaire, un granulome pyogénique, un syndrome de polypose juvénile, une fibrose pulmonaire idiopathique, une fibrose rénale, un rétrécissement postopératoire, la

formation de chéloïdes, une sclérodermie, et une fibrose cardiaque.

16. Composé selon l'une quelconque des revendications 1 à 6 ou composition selon la revendication 7, destiné(e) à une utilisation dans une méthode de traitement
d'une maladie cardiovasculaire, d'une dyslipidémie, d'une athérosclérose, d'une hypercholestérolémie, d'un syndrome métabolique, ou d'une maladie d'Alzheimer ;
d'une maladie ou d'une affection métabolique ; ou
d'une maladie ou d'une affection neurologique sélectionnée parmi la maladie d'Alzheimer, la maladie de Parkinson, la maladie de Huntington, un trouble bipolaire, la schizophrénie, le syndrome de Rubinstein-Taybi, et l'épilepsie.

17. Composé ou composition destiné(e) à une utilisation selon la revendication 16, l'affection métabolique étant sélectionnée parmi une inflammation associée à l'obésité, un diabète de type II, et une insulinorésistance.

REFERENCES CITED IN THE DESCRIPTION

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