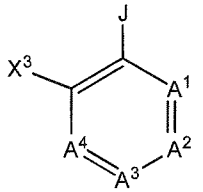
PYRIDINONE AND PYRIDAZINONE DERIVATIVES

BACKGROUND

Bromodomains refer to conserved protein structural folds which bind to N-acetylated lysine residues that are found in some proteins. The BET family of bromodomain containing proteins is comprised of four members (BRD2, BRD3, BRD4 and BRDt). Each member of the BET family employs two bromodomains to recognize N-acetylated lysine residues found primarily, but not exclusively, on the amino-terminal tails of histone proteins. These interactions modulate gene expression by recruiting transcription factors to specific genome locations within chromatin. For example, histone-bound BRD4 recruits the transcription factor P-TEFb to promoters, resulting in the expression of a subset of genes involved in cell cycle progression (Yang et al., Mol. Cell. Biol. 28: 967-976 (2008)). BRD2 and BRD3 also function as transcriptional regulators of growth promoting genes (LeRoy et al., Mol. Cell 30: 51-60 (2008)). BET family members were recently established as being important for the maintenance of several cancer types (Zuber et al., Nature 478: 524-528 (2011); Mertz et al; Proc. Nat'l. Acad. Sci. 108: 16669-16674 (2011); Delmore et al., Cell 146: 1-14, (2011); Dawson et al., Nature 478: 529-533 (2011)). BET family members have also been implicated in mediating acute inflammatory responses through the canonical NF-KB pathway (Huang et al., Mol. Cell. Biol. 29: 1375-1387 (2009)) resulting in the upregulation of genes associated with the production of cytokines (Nicodeme et al., Nature 468: 1119-1123, (2010)). The human immunodeficiency virus utilizes BRD4 to initiate transcription of viral RNA from stably integrated viral DNA (Jang et al., Mol. Cell, 19: 523-534 (2005). Thus, compounds that inhibit the binding of BET family bromodomains to their cognate acetylated lysine proteins are being pursued for the treatment of cancer, inflammatory diseases and some viral infections. Accordingly, there is an ongoing medical need to develop new drugs to treat these indications.

SUMMARY

In one aspect, the present ~~invention~~ disclosure relates to compounds of Formula (I) or a pharmaceutically acceptable salt thereof,



I

N-(4-(2,4-difluorophenoxy)-3-(4-(2-(dimethylamino)ethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(propan-2-yloxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-4-(2-methylpropoxy)-6-oxo-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(tetrahydrofuran-3-ylmethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-4-propoxy-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide; and

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(2,2,2-trifluoroethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide.

In certain embodiments, a compound of formula I is is selected from the group consisting of:

3-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]acetamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]acetamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide; and

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide

In another aspect, the present ~~invention~~ disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable exicipient and a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present ~~invention~~ disclosure relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need

thereof. In certain embodiments, the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present ~~invention~~ disclosure relates to methods of treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's

disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present ~~invention~~ disclosure relates to methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present ~~invention~~ disclosure relates to methods of treating obesity in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present ~~invention~~ disclosure relates to methods of treating type II diabetes in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament treating a disease or condition, wherein the medicament is to be administered to a subject in need thereof, wherein said disease or condition is selected from the group consisting

of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease,dermatitis, eczema,giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease,), Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis,myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating AIDS, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating obesity, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating type II diabetes, wherein the medicament is to be administered to a subject in need thereof.

DETAILED DESCRIPTION

a). Definitions

It is noted that, as used in this specification and the intended claims, the singular form "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a single compound as well as one or more of the same or different compounds, reference to "optionally a pharmaceutically acceptable carrier" refers to a single optional pharmaceutically acceptable carrier as well as

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]acetamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide; and

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

26. ~~A method for treating cancer in a subject comprising administering a therapeutically effective amount~~ Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof, in the manufacture of a medicament for treating cancer~~to a subject in need thereof~~, wherein the medicament is to be administered to a subject in need thereof.

27. The ~~method~~ use of claim 26 wherein the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous

leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

28. The ~~method~~ use of claim 27, ~~further comprising administering~~ wherein a therapeutically effective amount of at least one additional therapeutic agent is to be further administered.

29. ~~A method for treating a disease or condition in a subject comprising administering a therapeutically effective amount~~ Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating a disease or condition, wherein the medicament is to be administered to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease,dermatitis, eczema,giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease,), Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis,myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

30. The ~~method~~ useof claim 29, ~~further comprising administering~~wherein a therapeutically effective amount of at least one additional therapeutic agent is to be further administered.

31. ~~A method for treating AIDS in a subject comprising administering a therapeutically effective amount~~ Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating AIDS, wherein the medicament is to be administered to a subject in need thereof.

32. The ~~method~~ use of claim 31, ~~further comprising administering~~wherein a therapeutically effective amount of at least one additional therapeutic agent is to be further administered.

33. ~~A method for treating obesity in a subject comprising administering a therapeutically effective amount~~ Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating obesity, wherein the medicament is to be administered to a subject in need thereof.

34. The ~~method~~ use of claim 33, ~~further comprising administering~~wherein a therapeutically effective amount of at least one additional therapeutic agent is to be further administered.

35. ~~A method for treating type II diabetes in a subject comprising administering a therapeutically effective amount~~Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating type II diabetes, wherein the medicament is to be administered to a subject in need thereof.

36. The ~~method~~ use of claim 35, ~~further comprising administering~~wherein a therapeutically effective amount of at least one additional therapeutic agent is to be further administered.