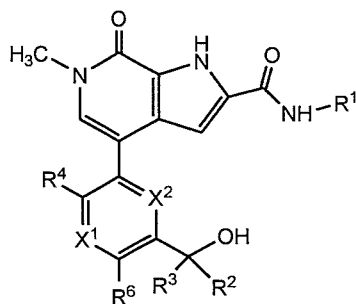


proteins are being pursued for the treatment of cancer, inflammatory diseases, kidney diseases, diseases involving metabolism or fat accumulation, and some viral infections, as well as for providing a method for male contraception. Accordingly, there is an ongoing medical need to develop new drugs to treat these indications.

5

SUMMARY

[0002] In one aspect the present disclosure provides for compounds of formula (I) or a pharmaceutically acceptable salt thereof,



(I),

10

wherein

R¹ is hydrogen, CD₂CD₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, a C₃-C₆ cycloalkyl, a phenyl, or a 5-6 membered monocyclic heteroaryl; wherein the C₃-C₆ cycloalkyl, the phenyl, and the 5-6 membered monocyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^x groups;

15

R² is G^{2a}, C₁-C₆ haloalkyl, or C₁-C₆ alkyl wherein the C₁-C₆ alkyl is optionally substituted with one substituent selected from the group consisting of G^{2b} and -OH; G^{2a} is a phenyl or a C₃-C₆ monocyclic cycloalkyl; wherein each G^{2a} is optionally substituted with 1, 2, 3, or 4 independently selected R^x groups;

G^{2b} is phenyl optionally substituted with 1, 2, 3, or 4 independently selected R^x

20

groups;

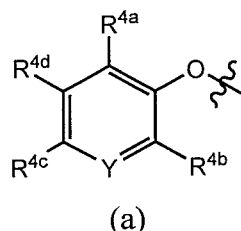
R³ is C₁-C₆ haloalkyl, C₁-C₆ alkyl, or a C₃-C₆ monocyclic cycloalkyl wherein the C₃-C₆ monocyclic cycloalkyl is optionally substituted with 1, 2, 3, or 4 independently selected R^x groups; or

25

R² and R³, together with the carbon atom to which they are attached, form a C₃-C₆ monocyclic cycloalkyl, a C₄-C₆ monocyclic cycloalkenyl, or a 4-6 membered monocyclic heterocycle; wherein the C₃-C₆ monocyclic cycloalkyl, the C₄-C₆ monocyclic cycloalkenyl, and the 4-6 membered monocyclic heterocycle are each optionally substituted with 1, 2, 3, or 4 independently selected R^x groups;

R⁴ is phenyl, pyridinyl, a C₃-C₆ monocyclic cycloalkyl, or a C₄-C₆ monocyclic cycloalkenyl; wherein each R⁴ is optionally substituted with 1, 2, 3, or 4 independently selected R^y groups; or

R⁴ is formula (a)



R^{4a} and R^{4b} are each independently halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R^{4c} and R^{4d} are each independently hydrogen, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -S(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), or -(C₁-C₆ alkylenyl)-OH;

10 Y is C(R^{4e}) or N; wherein R^{4e} is hydrogen, halogen, -CN, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R^x, at each occurrence, is independently halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R^y, at each occurrence, is independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -O(C₁-C₆ alkyl), -O(C₁-C₆ haloalkyl), or -(C₁-C₆ alkylenyl)-OH;

15 X¹ and X² are C(R⁵); or

one of X¹ and X² is N and the other is C(R⁵);

R⁵, at each occurrence, is independently hydrogen or halogen; and

R⁶ is hydrogen, halogen, -CN, C₁-C₆ haloalkyl, or C₁-C₆ alkyl.

20 [0003] Disclosed are methods for treating or preventing disorders that are ameliorated by inhibition of BET. Such methods comprise of administering to the subject a therapeutically effective amount of a compound of formula (I), alone, or in combination with a pharmaceutically acceptable carrier.

[0004] Some of the methods are directed to treating or preventing an inflammatory disease or cancer or AIDS.

25 [0004a] In another aspect, there is provided use of a compound of formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an acquired immunodeficiency syndrome (AIDS) in a subject in need thereof.

30 [0005] Disclosed are methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically 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 certain embodiments, the additional therapeutic agent is selected from the group consisting of cytarabine, bortezomib, and 5-azacitidine.

[0005a] In another aspect, there is provided use of a compound of formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0006] Disclosed are 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 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.

[0006a] In another aspect, there is provided use of a compound of formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition in 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.

[0007] Disclosed are methods of treating a chronic kidney disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease, and tubular interstitial nephritis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0007a] In another aspect, there is provided use of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a chronic kidney disease or condition in a subject in need thereof, wherein said chronic kidney disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis.

[0008] Disclosed are methods of treating an acute kidney injury or disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said acute kidney injury or disease or condition is selected from the group consisting of: ischemia-reperfusion induced kidney disease, cardiac and major surgery induced kidney disease, percutaneous coronary intervention induced kidney disease, radio-contrast agent induced kidney disease, sepsis induced kidney disease, pneumonia induced kidney disease, and drug toxicity induced kidney disease. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0008a] In another aspect, there is provided use of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an acute kidney disease or condition in a subject in need thereof, wherein said acute kidney disease or condition is selected from the group consisting of: ischemia-reperfusion induced kidney disease, cardiac and major surgery induced kidney disease, percutaneous coronary intervention induced kidney disease, radio-contrast agent induced kidney disease, sepsis induced kidney disease, pneumonia induced kidney disease, and drug toxicity induced kidney disease.

[0009] Disclosed are methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically 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.

[0010] Disclosed are methods of treating obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy, or diabetic neuropathy in a

subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically 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.

5 [0010a] In another aspect, there is provided use of a compound of formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein said disease or condition is selected from the group consisting of: obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin
10 resistance, diabetic retinopathy, and diabetic neuropathy.

[0011] Disclosed are methods of preventing conception by inhibiting spermatogenesis in a subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective
15 amount of at least one additional therapeutic agent.

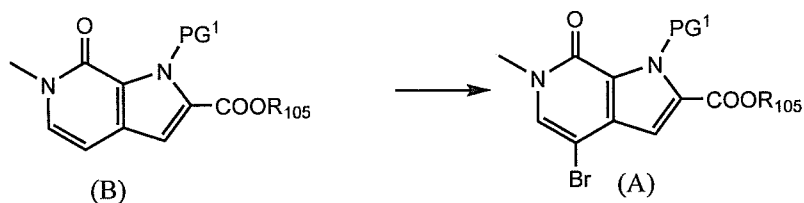
[0011a] In another aspect, there is provided use of a compound of formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contraception in a male subject in need thereof.

[0012] Disclosed is the use of a compound of formula (I), alone or in combination with at
20 least one additional therapeutic agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

[0013] Pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt, alone or in combination with at least one additional
25 therapeutic agent, are also provided.

[0013a] In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

30 [0013b] In another aspect, there is provided a process for preparing compounds of formula (A), wherein the process comprises bromination of compounds of formula (B)



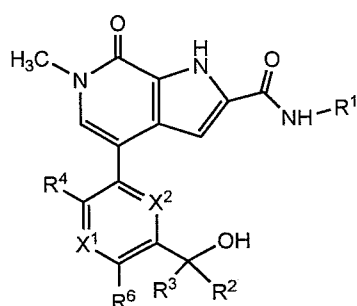
wherein

PG¹ is a nitrogen protecting group; and R₁₀₅ is C₁-C₆ alkyl.

5

DETAILED DESCRIPTION

[0014] Disclosed herein are compounds of formula (I)



(I)

10 wherein R¹, R², R³, R⁴, R⁶, X¹, and X² are defined above in the Summary of the Invention and below in the Detailed Description. Further, compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also disclosed.

15 [0015] Compounds disclosed herein may contain one or more variable(s) that occur more than one time in any substituent or in the formulae herein. Definition of a variable on each occurrence is independent of its definition at another occurrence. Further, combinations of

N-cyclopropyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl]-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxamide;

N-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(1-hydroxycyclobutyl)phenyl]-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxamide; and

N-ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(3-hydroxyoxetan-3-yl)phenyl]-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxamide.

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

22. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.

23. The use of claim 22 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.

24. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition in 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.

25. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an acquired immunodeficiency syndrome (AIDS) in a subject in need thereof.

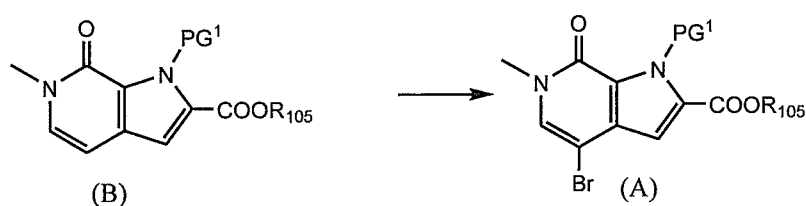
26. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein said disease or condition is selected from the group consisting of: obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy, and diabetic neuropathy.

27. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contraception in a male subject in need thereof.

28. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an acute kidney disease or condition in a subject in need thereof, wherein said acute kidney disease or condition is selected from the group consisting of: ischemia-reperfusion induced kidney disease, cardiac and major surgery induced kidney disease, percutaneous coronary intervention induced kidney disease, radio-contrast agent induced kidney disease, sepsis induced kidney disease, pneumonia induced kidney disease, and drug toxicity induced kidney disease.

29. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a chronic kidney disease or condition in a subject in need thereof, wherein said chronic kidney disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis.

30. A process for preparing compounds of formula (A), wherein the process comprises bromination of compounds of formula (B)



wherein

PG¹ is a nitrogen protecting group; and

R₁₀₅ is C₁-C₆ alkyl.

31. The process of claim 30 wherein PG¹ is selected from the group consisting of p-toluenesulfonyl, benzyl, and 2-(trimethylsilyl)ethoxymethyl.