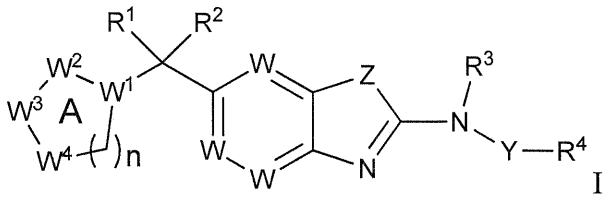
seminomas/dysgerminomas (Blume-Jensen *Nature* 2001 411(17): 355-365. KIT mutations have been also identified in certain melanomas and is recognized as a potential therapeutic target for melanoma (Curtain *et al. J Clin. Oncol.* 2006 24(26):4340-4346).

[0008] There continues to be a need for the identification of small molecules that inhibit RTKs, particularly compounds useful for the treatment of CSF1R-, FLT3, PDGFRβ- and/or KIT- mediated diseases.

SUMMARY

[0009] Provided herein are compounds of formula (I) or pharmaceutically acceptable salts, solvates, hydrates, clathrates, single stereoisomers, mixture of stereoisomers or racemic mixture of stereoisomers thereof. In certain embodiment, the compounds have activity as CSF1R, FLT3, KIT, and/or PDGFRβ kinase modulators. The compounds are useful in medical treatments, pharmaceutical compositions and methods for modulating the activity of CSF1R, FLT3, KIT, and/or PDGFRβ kinases, including wildtype and/or mutated forms of CSF1R, FLT3, KIT, and/or PDGFRβ kinases. In certain embodiments, the compounds provided herein have activity as CSF1R, FLT3, KIT, and/or PDGFRβ kinase modulators. In one embodiment, the compounds for use in the compositions and methods provided herein have formula (I).

[0010] In ~~certain embodiments~~one aspect, there is provided ~~herein are compounds~~ a compound of Formula I:



I

~~or pharmaceutically acceptable salts, solvates, hydrates, clathrates, single stereoisomers, mixture of stereoisomers or racemic mixture of stereoisomers thereof, wherein:~~

R^1 and R^2 are each independently selected from hydrogen, deuterium, halogen, hydroxyl and alkoxy, or R^1 and R^2 together form =O;

R^3 is hydrogen or alkyl;

groups selected from Q^2; and the remainder of R^{9a} or R^{11a} is hydrogen, deuterium or alkyl; and the remainder of R^{9b} or R^{11b} is hydrogen or Q^2; or

iii) R^{9a} and R^{10b}, R^{9b} and R^{10b}, R^{9b} and R^{10a}, R^{9b} and R^{10a}, R^{10b} and R^{11a}, R^{10a} and R^{11b}, R^{10a} and R^{11b} or R^{10b} and R^{11b} together with the atoms to which they are attached form an aryl, heteroaryl or heterocyclyl ring optionally fused to a phenyl ring optionally substituted with one or more, in one embodiment, one to three, in another embodiment, one, two or three groups selected from Q^2; and the remainder of R^{9a} or R^{11a} is hydrogen, , deuterium or alkyl and the remainder of R^{9b} or R^{11b} is hydrogen or Q^2;

each Q^2 is independently halo, deuterium, cyano, oxo, thioxo, alkyl, haloalkyl, haloalkenyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$,$-R^uOR^uN(R^y)(R^z)$, $R^uN(R^y)(R^z)$, $-R^uSR^x$, $-R^uC(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)R^uN(R^y)(R^z)$, $-R^uC(J)N(R^y)OR^x$, $-C(=NOR^x)R^x$, $-R^uS(O)_tR^w$, $-R^uN(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)S(O)_tR^w$ or $-C(=NR^y)N(R^y)OR^x$, where the alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl groups are optionally substituted with one or more groups Q^4; in one embodiment, one to three Q^4 groups, each Q^4 is independently selected from halo, deuterium, hydroxyl, alkyl, haloalkyl and hydroxyalkyl;

~~each~~ R^d is independently hydrogen or alkyl;

each R^u is independently alkylene, alkenylene or a direct bond;

R^w is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

each R^x is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

R^y and R^z are each independently selected from (i) or (ii) below:

(i) R^y and R^z are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or

(ii) R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl, optionally substituted with one or more, in one embodiment, one, two or three Q^7 groups; each Q^7 is independently selected from halo, deuterium, oxo, thioxo, hydroxy, alkoxy, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl;

J is O, NR^x or S;

each t is independently an integer from 0-2;

n is 1 or 2; and

q is an integer from 0-4,

wherein the compounds are selected such that: i) when W is CH; W^1 is C; Z is S; R^1 is hydrogen, or hydroxyl and R^2 is hydrogen, or R^1 and R^2 together form =O; then ring A is not pyridine; ii) when W is CH; W^1 is N; Z is S; R^1 and R^2 are hydrogen, then ring A is not pyrrolidine; iii) when W is CH, Z is NH, R^1 and R^2 together form =O, q is 0, and R^4 is pyridinyl, then ring A is not phenyl, iv) when W is CH, Z is NH, R^1 and R^2 together form =O, q is 0, and R^4 is phenyl, then ring A is not pyrrolidine, and v) when Z is N, one of R^1 and R^2 is methyl and the other of R^1 and R^2 is H, q is 0, and R^3 is pyridine, and W^1 is N, ring A cannot be piperidine, 1,2,3,4-tetrahydroisoquinoline, or isoindoline.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable carrier.

[0011] In one embodiment, the compound provided herein is a compound of formula (I). In one embodiment, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I). In one embodiment, the compound provided herein is a solvate of the compound of formula (I). In one embodiment, the compound provided herein is a hydrate of compound of formula (I). In one embodiment, the compound provided herein is a prodrug of the compound of formula (I). In one embodiment, the compound provided herein is a clathrate of the compound of formula (I).

[0012] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof, and optionally comprising at least one pharmaceutical carrier.

delivery, or for local or topical application are administered to an individual exhibiting the symptoms of the disease or disorder to be treated. The amounts are effective to ameliorate or eliminate one or more symptoms of the disease or disorder.

In another aspect, there is provided a compound as defined above for use in the treatment of a disease selected from an inflammatory disease, an inflammatory condition, an autoimmune disease and cancer.

In another aspect, there is provided a compound as defined above for use in the treatment of a disease selected from myeloproliferative disorder (MPD), myelodysplasia syndrome (MDS), polycythemia vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM), idiopathic myelofibrosis (IMF), myeloid leukemia, chronic myeloid leukemia (CML), imatinib-resistant CML, acute myeloid leukemia (AML), acute megakaryoblastic leukemia (AMKL), lymphoma, Hodgkin's lymphoma, lymphoblastic leukemia, myeloma, multiple myeloma, cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, endometrial cancer, melanoma, lung cancer, brain cancer, thyroid cancer, stomach cancer, gastrointestinal stromal tumor, colorectal cancer, pancreatic cancer, renal cancer, non-small cell lung cancer, bone cancer, tenosynovial giant cell tumors, glioblastoma multiforme, atherosclerosis, restenosis, obliterative bronchiolitis, idiopathic myelofibrosis, obesity, obesity-induced insulin resistance, hypercalcemia of malignancy, lupus nephritis, glomerular nephritis, idiopathic hypereosinophilic syndrome, chronic eosinophilic syndrome, systemic mastocytosis, Langerhans cell histiocytosis, Kaposi's sarcoma, multiple endocrine neoplasia, immunodeficiency, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), cutaneous lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, osteoporosis, endometriosis, asthma, allergic asthma, ankylosing spondylitis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease and multiple sclerosis.

In another aspect, there is provided use of a compound as defined above for the manufacture of a medicament for the treatment of a disease selected from myeloproliferative disorder (MPD), myelodysplasia syndrome (MDS), polycythemia

vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM), idiopathic myelofibrosis (IMF), myeloid leukemia, chronic myeloid leukemia (CML), imatinib-resistant CML, acute myeloid leukemia (AML), acute megakaryoblastic leukemia (AMKL), lymphoma, Hodgkin's lymphoma, lymphoblastic leukemia, myeloma, multiple myeloma, cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, endometrial cancer, melanoma, lung cancer, brain cancer, thyroid cancer, stomach cancer, gastrointestinal stromal tumor, colorectal cancer, pancreatic cancer, renal cancer, non-small cell lung cancer, bone cancer, tenosynovial giant cell tumors, glioblastoma multiforme, atherosclerosis, restenosis, obliterative bronchiolitis, idiopathic myelofibrosis, obesity, obesity-induced insulin resistance, hypercalcemia of malignancy, lupus nephritis, glomerular nephritis, idiopathic hypereosinophilic syndrome, chronic eosinophilic syndrome, systemic mastocytosis, Langerhans cell histiocytosis, Kaposi's sarcoma, multiple endocrine neoplasia, immunodeficiency, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), cutaneous lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, osteoporosis, endometriosis, asthma, allergic asthma, ankylosing spondylitis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease and multiple sclerosis.

In another aspect, there is provided a compound as defined above for use in modulating a CSF1R, FLT3, KIT, and/or PDGFR kinase.

In another aspect, there is provided use of a compound as defined above for the manufacture of a medicament for treating a disease selected from an inflammatory disease, an inflammatory condition, an autoimmune disease and cancer.

[0019] Further provided is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency

of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (e.g., separately, sequentially or concurrently), or the like.

[0020] These and other ~~aspects~~ embodiments of the subject matter described herein will become evident upon reference to the following detailed description.

BRIEF DESCRIPTION OF THE DRAWING

[0021] Fig. 1 depicts the *in vivo* inhibition of CSF-1 dependent M-NFS-60 tumor cell proliferation in the peritoneal cavity of athymic nu/nu mice from the administration of one of the compounds provided herein having the Formula I (Compound A).

[0022] Fig. 2 depicts the *in vivo* inhibition of CSF-1 dependent M-NFS-60 tumor cell proliferation in the peritoneal cavity of athymic nu/nu mice from the administration of one of the compounds provided herein having the Formula I (Compound B).

[0023] Fig. 3 depicts the *in vivo* inhibition of PTHrP-induced hypercalcemia from the administration of Compound A having the Formula I, in BDF1 mice challenged twice daily for seven days with 0.5 mg/kg recombinant PTHrP, as measured by serum TRAPC5B levels, a bone resorption marker.

[0024] Fig. 4 depicts the *in vivo* inhibition of PTHrP-induced hypercalcemia from the administration of Compound B having the Formula I, in BDF1 mice challenged twice daily for seven days with 0.5 mg/kg recombinant PTHrP, as measured by serum TRAPC5B levels, a bone resorption marker.

[0025] Fig. 5 depicts the *in vivo* inhibition of MCP-1 induction in Balb/c mice treated with Compound A having the Formula I, prior to M-CSF stimulation.

24. A pharmaceutical composition comprising a compound of any of claims 1-22 and a pharmaceutically acceptable carrier.

25. A ~~method~~compound of any of claims 1-22 for use in the treatment of a disease selected from an inflammatory disease, an inflammatory condition, an autoimmune disease and cancer ~~comprising administering a therapeutically effective amount of a compound of any of claims 1-22~~.

26. The ~~method~~compound of claim 24, wherein the disease is modulated by CSF1R, FLT3, KIT, and/or PDGFRp kinase.

27. The ~~method~~compound of claim 25, wherein the disease is modulated by wild type or mutant CSF1R, FLT3, KIT, and/or PDGFRp kinase.

28. A ~~method~~compound of any of claims 1-22 for use in the treatment of a disease ~~comprising administering a therapeutically effective amount of a compound of any of claims 1-22, wherein the disease is~~ selected from myeloproliferative disorder (MPD), myelodysplasia syndrome (MDS), polycythemia vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM), idiopathic myelofibrosis (IMF), myeloid leukemia, chronic myeloid leukemia (CML), imatinib-resistant CML, acute myeloid leukemia (AML), acute megakaryoblastic leukemia (AMKL), lymphoma, Hodgkin's lymphoma, lymphoblastic leukemia, myeloma, multiple myeloma, cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, endometrial cancer, melanoma, lung cancer, brain cancer, thyroid cancer, stomach cancer, gastrointestinal stromal tumor, colorectal cancer, pancreatic cancer, renal cancer, non-small cell lung cancer, bone cancer, tenosynovial giant cell tumors, glioblastoma multiforme, atherosclerosis, restenosis, obliterative bronchiolitis, idiopathic myelofibrosis, obesity, obesity-induced insulin resistance, hypercalcemia of malignancy, lupus nephritis, glomerular nephritis, idiopathic hypereosinophilic syndrome, chronic eosinophilic syndrome, systemic mastocytosis, Langerhans cell histiocytosis, Kaposi's sarcoma, multiple endocrine neoplasia, immunodeficiency, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes,

sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), cutaneous lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, osteoporosis, endometriosis, asthma, allergic asthma, ankylosing spondylitis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease and multiple sclerosis.

29. Use of a compound of any of claims 1-22 for the manufacture of a medicament for the treatment of a disease selected from myeloproliferative disorder (MPD), myelodysplasia syndrome (MDS), polycythemia vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM), idiopathic myelofibrosis (IMF), myeloid leukemia, chronic myeloid leukemia (CML), imatinib-resistant CML, acute myeloid leukemia (AML), acute megakaryoblastic leukemia (AMKL), lymphoma, Hodgkin's lymphoma, lymphoblastic leukemia, myeloma, multiple myeloma, cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, endometrial cancer, melanoma, lung cancer, brain cancer, thyroid cancer, stomach cancer, gastrointestinal stromal tumor, colorectal cancer, pancreatic cancer, renal cancer, non-small cell lung cancer, bone cancer, tenosynovial giant cell tumors, glioblastoma multiforme, atherosclerosis, restenosis, obliterative bronchiolitis, idiopathic myelofibrosis, obesity, obesity-induced insulin resistance, hypercalcemia of malignancy, lupus nephritis, glomerular nephritis, idiopathic hypereosinophilic syndrome, chronic eosinophilic syndrome, systemic mastocytosis, Langerhans cell histiocytosis, Kaposi's sarcoma, multiple endocrine neoplasia, immunodeficiency, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), cutaneous lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, osteoporosis, endometriosis, asthma, allergic asthma, ankylosing spondylitis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease and multiple sclerosis.

~~29~~30. The ~~method~~compound of claim 27 further comprising ~~administering~~ a second pharmaceutical agent selected from anti-proliferative agent, anti-inflammatory agent, immunomodulatory agent and immunosuppressive agent.

~~30~~31. A compound of any of claims 1-22~~method of~~ for use in modulating a CSF1R, FLT3, KIT, and/or PDGFR kinase~~ by administering a compound of any of claims 1-22~~.

~~31~~32. Use of ~~A~~a compound of any of claims 1-22 for the manufacture of a medicament for treating a disease selected from an inflammatory disease, an inflammatory condition, an autoimmune disease and cancer.

33. The use of claim 32, wherein the disease is modulated by CSF1R, FLT3, KIT, and/or PDGFRp kinase.

34. The use of claim 33, wherein the disease is modulated by wild type or mutant CSF1R, FLT3, KIT, and/or PDGFRp kinase.