serine/threonine protein kinase or a fragment or a complex thereof or a functional equivalent thereof and a PI3K kinase or a fragment or a complex thereof or a functional equivalent thereof, prevents, inhibits or ameliorates a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound as defined above.

In some embodiments, the conditions are cancer, angiogenic disorder or pathological angiogenesis, fibrosis, inflammatory conditions, asthma, neurological disorders, neurodegenerative disorders, muscle degenerative disorders, autoimmune disorders, disorders of the blood or disorders of the bone marrow. In some embodiments the cancer is selected from the group consisting of hematologic cancer and solid tumor such as myeloproliferative disorders (idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukemia, acute lymphocytic leukemia, acute erythroblastic leukemia, Hodgkin's and Non Hodgkin's disease, B-cell lymphoma, diffuse large B cell lymphoma, acute T-cell leukemia, myelodysplastic syndromes, plasma cell disorder, hairy cell leukemia, kaposi's sarcoma, lymphoma; gynaecologic cancer such as breast carcinoma, ovarian cancer, cervical cancer, vaginal and vulva cancer, endometrial hyperplasia; gastrointestinal tract cancer such as colorectal carcinoma, polyps, liver cancer, gastric cancer, pancreatic cancer, gall bladder cancer; urinary tract cancer such as prostate cancer, kidney and renal cancer; urinary bladder cancer, urethral cancer, penile cancer; skin cancer such as melanoma; brain tumour such as glioblastoma, neuroblastoma, astrocytoma, ependynoma, brain-stem gliomas, medulloblastoma, menigiomas, astrocytoma, oligodendroglioma; head and neck cancer such as nasopharyngeal carcinoma, laryngeal carcinoma; respiratory tract cancer such as lung carcinoma (NSCLC and SCLC), mesothelioma; eye disease such as retinoblastoma; musculo-skeleton diseases such as osteosarcoma, musculoskeleletal neoplasm; Squamous cell carcinoma and fibroid tumour.

In further embodiments, there is provided a use of the compound as defined above to inhibit one or more deacetylase(s) selected from the group consisting of HDACs and non-histone deacetylase or a fragment or a complex thereof or a functional equivalent thereof.

In even further embodiments, there is provided a use of the compound as defined above to inhibit one or more protein kinase(s) selected from the group consisting of a serine/threonine protein kinase or a fragment or a complex thereof or a functional equivalent thereof and a Akt or mTOR kinase or a fragment or a complex thereof or a functional equivalent thereof.

In some embodiments, the protein kinase is a PI3K kinase or a fragment thereof or a complex thereof or a functional equivalent thereof. In some embodiments the PI3K kinase or a fragment thereof or a complex thereof or a functional equivalent thereof, is a class I PI3K or a fragment thereof or a complex thereof or a functional equivalent thereof.

In a third aspect, there is provided a method of inhibiting HDAC and/or PI3K in a cell in vitro comprising administering to a cell a compound as defined above, or a pharmaceutically acceptable form or prodrug thereof.

In some embodiments, there is provided a method of prevention or treatment of a proliferative condition in a subject, the method including administration of a therapeutically effective amount of a compound as defined above.

In ~~a fourth aspect~~the present disclosure, there is provided a method of treating a HDAC- or PI3K-related disorder comprising administering to a subject in need of treatment a compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or a composition as defined above.

In ~~a fifth aspect~~the present disclosure, there is provided a method of treating a HDAC- and PI3K-related disorder comprising administering to a subject in need of treatment a compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or a composition as defined above.

In ~~an sixth aspect~~the present disclosure, there is provided a method of modulating the self-renewal or differentiation of stem-cells comprising administering to a subject in need of treatment a compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or a composition as defined above.

In further embodiments, there is provided a use of the compound as defined above in the preparation of a medicament for treating a condition in an animal in which inhibition one or more deacetylase(s) selected from the group consisting of HDACs and non-histone deacetylase or a fragment or a complex thereof or a functional equivalent thereof, prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

In further embodiments there is provided a use of the compound as defined above in the preparation of a medicament for treating a condition in an animal in which inhibition of one or more protein kinase(s) selected from the group consisting of a serine/threonine protein kinase or a fragment or a complex thereof or a functional equivalent thereof and a PI3K kinase or a fragment or a complex thereof or a functional equivalent thereof, prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

In a fourth ~~seventh~~ aspect, there is provided a use of the compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or the composition as defined above, in the manufacture of a medicament for treatment of a HDAC- or PI3K-related disorder.

In a~~n~~ fifth ~~eighth~~ aspect, there is provided a use of the compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or the composition as defined above in the manufacture of a medicament for treatment of a HDAC- and PI3K-related disorder.

In a sixth ~~ninth~~ aspect, there is provided a use of the compound as defined above, or a pharmaceutically acceptable form or prodrug thereof, or the composition as defined above, in the manufacture of a medicament for modulating the self-renewal or differentiation of stem-cells.

In further embodiments, there is provided a use of the compound as defined above or a pharmaceutically acceptable salt, N-oxide or prodrug thereof in the treatment of a condition in which inhibition of one or more protein kinase(s) selected from the group consisting of a serine/threonine protein kinase or a fragment or a complex thereof or a functional equivalent thereof and a PI3K kinase or a fragment or a complex thereof or a functional equivalent thereof, prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

In some embodiments the protein kinase is a serine/threonine protein kinase or a fragment or a complex thereof or a functional equivalent thereof. In some embodiments the serine/threonine protein kinase or a fragment or complex thereof is an mTOR protein kinase or a fragment thereof, or a complex thereof or a functional equivalent thereof. In some embodiments the serine/threonine protein kinase is mTORC1 or a fragment or complex thereof or a functional equivalent thereof.

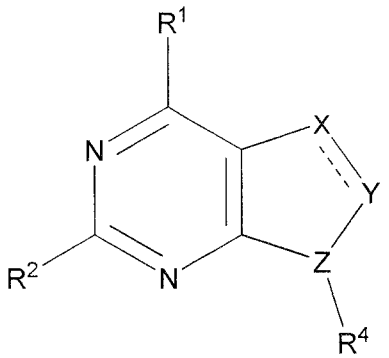
Advantageously, these compounds also modulated biological drug targets in tumor models. The compounds induced histone hyperacetylation in PC-3 prostate tumors when orally dosed in tumor-bearing mice and induced histone hyperacetylation in MV4-11 xenograft tumors via different routes of administration. The compound also demonstrated excellent antitumor activity in HCC models such as NCr nude mice HepG2 xenograft model and CB17 scid mice HepG2 xenograft model as well as HuH-7 HCC xenograft model. The compound was also demonstrated to have broad antitumor activity in a number of xenograft models when dosed orally in 4T1 mouse metastatic breast cancer model, NCI-H460 lung cancer xenograft model and MV4-11 leukaemia xenograft model.

The disclosure further relates to a process for synthesizing the compound of formula (I) and its precursors.

In a seventh ~~tenth~~ aspect, there is provided a process for synthesizing the compound of formula (I) comprising the steps of; (a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound; (b) alkylating the amine (-NH- group) in the compound of step (a); (c) selectively or sequentially displacing the halide atoms of the intermediary compound of step (b) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (d) selectively coupling the intermediary compound of step (c) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and (e) converting the protected hydroxamate or the ester of the intermediary compound of step (d) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

In an eighth ~~eleventh~~ aspect, there is provided a process for synthesizing the compound of formula (I), comprising the steps of; (a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound; (b) selectively displacing one of the halide atoms of said compound with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (c) alkylating the amine (-NH- group) in the intermediary compound of step (b); (d) selectively displacing the remaining halide atom of the intermediary compound of step (c) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (e) selectively coupling the intermediary compound of step (d) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and (f) converting the protected hydroxamate or the ester of the intermediary compound of step (e) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

In a ninth ~~twelfth~~ aspect, there is provided a process for synthesizing the compound of formula (I);



(I)

comprising the steps of; (a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound; (b) alkylating the amine in the compound of step (a); (c) selectively or sequentially displacing the halide atoms of the intermediary compound of step (b) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (d) alkylating, in the intermediary compound of step (c), the carbon atom that corresponds to the Y-position of formula (I); (e) selectively coupling the intermediary compound of step (d) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic ester precursor); and (f) converting the protected hydroxamate or the ester of the intermediary compound of step (e) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

In a tenth ~~thirteenth~~ aspect, there is provided a process for synthesizing the compound of formula (I), comprising the steps of; (a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound; (b) selectively displacing one of the halide atoms of said compound with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (c) alkylating the amine (-NH- group) in the intermediary compound of step (b); (d) alkylating, in the intermediary compound of step (c), the carbon atom that corresponds to the Y-position of formula (I); (e) selectively displacing the remaining halide atom of the intermediary compound of step (d) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively; (f) selectively coupling the compound of step (e) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and (g) converting the protected hydroxamate or the ester of the intermediary compound of step (f) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

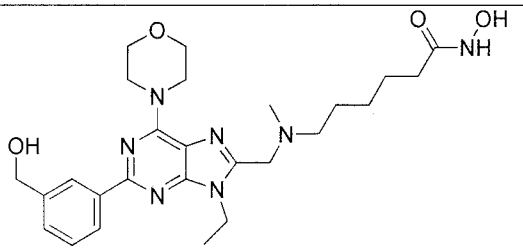
These and other features of the present teachings are set forth herein.

## Definitions

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined. The following words and terms used herein shall have the meaning indicated:

In the definitions of a number of substituents below it is stated that "the group may be a terminal group or a bridging group". This is intended to signify that the use of the term is intended to encompass the situation where the group is a linker between two other portions of the molecule as well as where it is a terminal moiety. Using the term alkyl as an example, some publications would use the term "alkylene" for a bridging group and hence in these other publications there is a distinction between the terms "alkyl" (terminal group) and "alkylene" (bridging group). In the present application no such distinction is made and most groups may be either a bridging group or a terminal group.

"Acyl" means an R-C(=O)- group in which the R group may be an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted

| EX | Chemical Structure and Name |
|---|---|
| 97 |  6-(((9-ethyl-2-(3-(hydroxymethyl)phenyl)-6-morpholino-9*H*-purin-8-yl)methyl)(methyl)amino)-*N*-hydroxyhexanamide |

or a pharmaceutically acceptable salt or prodrug thereof.

39. The compound according to any of the preceding claims, wherein the compound is an enzyme inhibitor.

40. The compound according to claim 39, wherein the compound is a histone deacetylase (HDAC) inhibitor.

41. The compound according to claim 39, wherein the compound is a phosphatidylinositide-3-kinase (PI3K) inhibitor.

42. The compound according to any one of claims 1 to 38, wherein the compound is an inhibitor of the PI3K-AKT-mTOR pathway.

43. The compound according to any one of claims 1 to 38, wherein the compound is a multi-target inhibitor.

44. The compound according to claim 43, wherein the compound inhibits HDAC and PI3K simultaneously.

45. A pharmaceutical composition comprising a compound of any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, and a pharmaceutically acceptable excipient.

46. A method of inhibiting HDAC and/or PI3K in a cell in vitro comprising administering to a cell a compound of any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof.

47. The method according to claim 46, wherein the inhibition of HDAC and/or PI3K further comprises the inhibition of cell proliferation.

48. The method according to claim 46, wherein the inhibition of HDAC and/or PI3K further comprises reprogramming cells to induce pluripotent stem cells (iPS cells).

~~49. The method according to claims 46 or 47, wherein the cell is in vitro.~~

~~50~~49. The method according to claim ~~49~~46, wherein the cell is from a cell line.

~~51~~50. The method according to claim ~~50~~49, wherein the cell line is an immortalized cell line, a genetically modified cell line or a primary cell line.

~~52~~51. The method according to claim ~~51~~50, wherein the cell line is selected from the group consisting of MV4-11, MOLT-4, PC-3, MCF-7, SUP-B15, HL-60, K-562, RPMI-8226, Daudi, Raji, Ramos, Pfeiffer, A431, ACHN, A549, COLO 205, HCT116, HEL92.1.7, NCI-H522, A375, NCI-H460, BxPC-3, PANC-1, SK-OV-3,U87MG, U138MG, HpeG2, SK-HEP1, HuH-7, HCCLM3, PLC/PRF/5, HeLa, BT 474, MDA-MB-231, MDA-MB-436 and MDA-MB-468.

~~53~~52. The method according to claim 46 or 47 wherein the cell is obtained from tissue of a subject.

~~54. The method according to claims 46 or 47, wherein the cell is in a subject.~~

~~55. A method of treating a HDAC- or PI3K-related disorder comprising administering to a subject in need of treatment a compound of any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45.~~

~~56. A method of treating a HDAC- and PI3K-related disorder comprising administering to a subject in need of treatment a compound of any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45.~~

~~57. The method according to claims 55 or 56, wherein the disorder is cancer, angiogenic disorder or pathological angiogenesis, fibrosis, inflammatory conditions, asthma, neurological disorders, neurodegenerative disorders, muscle degenerative disorders, autoimmune disorders, disorders of the blood or disorders of the bone marrow.~~

~~58. The method according to claim 57, wherein the disorder is lymphoma, cutaneous T-cell lymphoma, follicular lymphoma, or Hodgkin lymphoma, cervical cancer, ovarian cancer, breast cancer, lung cancer, prostate cancer, colorectal cancer, sarcoma, hepatocellular carcinoma, leukemia or myeloma, retinal angiogenic disease, liver fibrosis, kidney fibrosis, Alzheimer's disease or Huntington's disease, spinal muscular atrophy, HIV/AIDS, polycythemia vera or essential thrombocythemia or myelofibrosis.~~

~~59. The method according to any one of claims 55 to 57, further comprising the step of administering an additional therapeutic agent in the subject.~~

~~60. A method of modulating the self-renewal or differentiation of stem cells comprising administering to a subject in need of treatment a compound of any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45.~~

~~61~~53. The compound according to any one of claims 1 to 37, or a pharmaceutically form or prodrug thereof, or a composition according to claim 45, for use in therapy.

~~62~~54. A use of a compound according to any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45, in the manufacture of a medicament for treatment of a HDAC- or PI3K-related disorder.

~~63~~55. A use of a compound according to any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45, in the manufacture of a medicament for treatment of a HDAC- and PI3K-related disorder.

~~64~~56. The use according to claims ~~62~~54 or ~~63~~55, wherein the disorder is cancer, angiogenic disorder or pathological angiogenesis, fibrosis, inflammatory conditions, asthma, neurological disorders, neurodegenerative disorders, muscle degenerative disorders, autoimmune disorders, disorders of the blood or disorders of the bone marrow.

~~65~~57. The use according to claim ~~64~~56, wherein the disorder is lymphoma, cutaneous T-cell lymphoma, follicular lymphoma, or Hodgkin lymphoma, cervical cancer, ovarian cancer, breast cancer, lung cancer, prostate cancer, colorectal cancer, sarcoma, hepatocellular carcinoma, leukemia or myeloma, retinal angiogenic diseases, liver and kidney fibrosis, Alzheimer's disease or Huntington's disease, spinal muscular atrophy, HIV/AIDS, polycythemia vera or essential thrombocythemia or myelofibrosis.

~~66~~58. The use according to any one of claims ~~62~~-54 to ~~65~~57, wherein the medicament is administered with an additional therapeutic agent, wherein said medicament is to be administered in combination or alteration with the additional therapeutic agent.

~~67~~59. A use of a compound according to any one of claims 1 to 38, or a pharmaceutically acceptable form or prodrug thereof, or a composition according to claim 45, in the manufacture of a medicament for modulating the self-renewal or differentiation of stem-cells.

~~68~~60. A process for synthesizing the compound of formula (I) comprising the steps of;

(a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound;

(b) alkylating the amine (-NH- group) in the compound of step (a);

(c) selectively or sequentially displacing the halide atoms of the intermediary compound of step (b) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

(d) selectively coupling the intermediary compound of step (c) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and

(e) converting the protected hydroxamate or the ester of the intermediary compound of step (d) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

~~69~~61. A process for synthesizing the compound of formula (I), comprising the steps of;

(a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound;

(b) selectively displacing one of the halide atoms of said compound with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

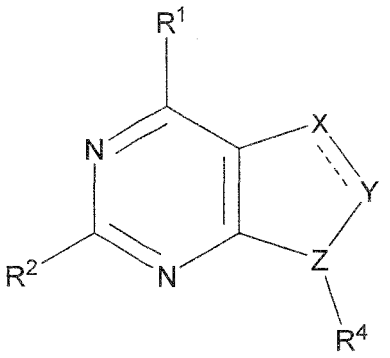
(c) alkylating the amine (-NH- group) in the intermediary compound of step (b);

(d) selectively displacing the remaining halide atom of the intermediary compound of step (c) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

(e) selectively coupling the intermediary compound of step (d) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and

(f) converting the protected hydroxamate or the ester of the intermediary compound of step (e) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

~~7062~~. A process for synthesizing the compound of formula (I);




(I)

comprising the steps of;

(a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound;

(b) alkylating the amine in the compound of step (a);

(c) selectively or sequentially displacing the halide atoms of the intermediary compound of step (b) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

(d) alkylating, in the intermediary compound of step (c), the carbon atom that corresponds to the Y-position of formula (I);

(e) selectively coupling the intermediary compound of step (d) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic ester precursor); and

(f) converting the protected hydroxamate or the ester of the intermediary compound of step (e) to a hydroxamic acid under reaction conditions to form the compound of formula (I).

~~71~~563. A process for synthesizing the compound of formula (I), comprising the steps of;

(a) providing a halogen-disubstituted purine-based or halogen di-substituted fused pyrimidine-based compound;

(b) selectively displacing one of the halide atoms of said compound with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

(c) alkylating the amine (-NH- group) in the intermediary compound of step (b);

(d) alkylating, in the intermediary compound of step (c), the carbon atom that corresponds to the Y-position of formula (I);

(e) selectively displacing the remaining halide atom of the intermediary compound of step (d) with an optionally substituted boronic ester or an optionally substituted amine to form a substituted aromatic or a substituted amine, respectively;

(f) selectively coupling the compound of step (e) with a protected hydroxamic acid group having the structure $-L^1-R^5-L^2-R^6-L^3-CON(R^a)OR^b$ or an ester (hydroxamic acid precursor); and

(g) converting the protected hydroxamate or the ester of the intermediary compound of step (f) to a hydroxamic acid under reaction conditions to form the compound of formula (I).