Trends in Biochemical Sciences 33(3): 122-131), prostate cancer (Tam *et al.*, 2007, British Journal of Cancer, 97, 378 – 383) These results indicate that inhibitors of JAK, in particular of JAK1 and/or JAK2, may also have utility in the treatment of cancers (leukaemias and solid tumours e.g. uterine leiomyosarcoma, prostate cancer).

[0021] In addition, Castleman's disease, multiple myeloma, mesangial proliferative glomerulonephritis, psoriasis, and Kaposi's sarcoma are likely due to hypersecretion of the cytokine IL-6, whose biological effects are mediated by intracellular JAK-STAT signaling (Tetsuji Naka, Norihiro Nishimoto and Tadamitsu Kishimoto, Arthritis Res 2002, 4 (suppl 3):S233-S242). This result shows that inhibitor of JAK, may also find utility in the treatment of said diseases.

[0022] A link with autoimmune diseases has been established for JAK3 and Tyk2. Mutations in JAK3 but also in the upstream signaling components gamma-c receptor chain and IL7 receptor account in aggregate for ~70% of cases of human severe combined immunodeficiency ('OShea *et al.*, 2004). Note that JAK1 cooperates with JAK3 in transducing signals from the gamma-c receptor chain. Tyk2 polymorphisms are seen in systemic lupus erythematosus (SLE) (O'Sullivan *et al*, 2007, Mol Immunol. 44(10):2497-506). Hence, targeting the JAK family may provide a therapeutic opportunity in the immuno-inflammation area.

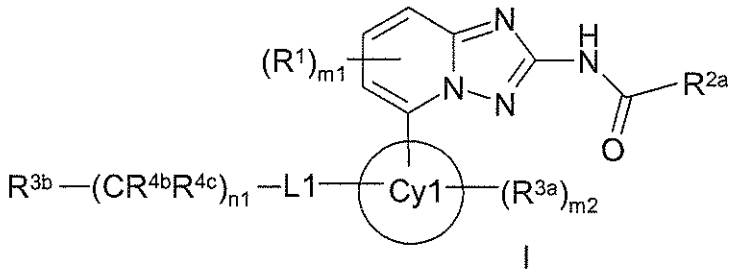
[0023] The current therapies are not satisfactory and therefore there remains a need to identify further compounds that may be of use in the treatment of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). The present invention therefore provides compounds, methods for their manufacture and a pharmaceutical comprising a compound of the invention together with a suitable pharmaceutical carrier. The present invention also provides for the use of a compound of the invention in the preparation of a medicament for the treatment of degenerative joint diseases.

SUMMARY OF THE INVENTION

[0024] The present ~~invention~~disclosure is based on the discovery that inhibitors of JAK are useful for the treatment of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease,

rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). The present ~~invention~~disclosure also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating diseases involving cartilage degradation, joint degradation and/or inflammation by administering a compound of the invention.

[0025] Accordingly, in one example~~a first aspect of the invention~~, 1,2,4-triazolo[1,5-a]pyridine compounds are disclosed having a Formula (I):



I

wherein

Cy1 is selected from aryl and heteroaryl;

L1 is selected from a single bond, -O-, -C(O)-, -C[=N(R^{4a})]-, -N(R^{4a})-, -CON(R^{4a})-, -SO_2N(R^{4a})-, -$S(O)_2$-, - N(R^{4a})CO-, -CH_2-N(R^{4a})- or - N(R^{4a})SO_2-;

each R^1 is independently selected from C_1-C_6 alkyl, substituted C_1-C_6 alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted amido, substituted or unsubstituted amino, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxyl;

each R^{3a} is independently selected from C_1-C_6 alkyl, substituted C_1-C_6 alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted amido, alkoxycarbonyl, substituted alkoxycarbonyl, arylalkyloxy, substituted arylalkyloxy, substituted or unsubstituted amino, aryl, substituted aryl, arylalkyl, substituted sulfanyl, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, substituted or

unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl, nitro, and thiol;

R^{2a} is selected from substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted C_3-C_7 cycloalkyl;

R^{3b} is independently selected from substituted or unsubstituted aryl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted 5-10 membered heteroaryl; or R^{3b} is independently selected from O-R^{3c}, NH-R^{3c}, CO-R^{3c}, and CON(R^{4a})-R^{3c}; and R^{3c} is independently selected from substituted C_1-C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted 5-10 membered heteroaryl;

each R^{4a}, R^{4b} and R^{4c} is independently selected from H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_7 cycloalkyl, or substituted C_3-C_7 cycloalkyl, substituted or unsubstituted acyl;

m1 is 0, 1, or 2; m2 is 0, 1, 2, or 3; and n1 is 0, 1, 2, 3, or 4;

provided that

i) when L1 is –O-, -N(R^{4a})-, -CH_2-N(R^{4a})-, -CON(R^{4a})-, or -SO_2N(R^{4a})-, and R^{3b} is other than cycloalkyl, aryl or 5-10 membered heteroaryl, then n1 is 1, 2, 3, or 4;

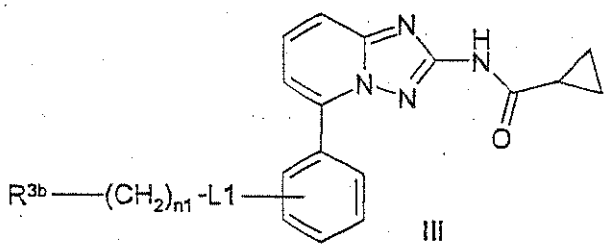
ii) when Cy1 is Ph, L1 is a bond, n1 is 0, and R^{3b} is –OR^{3c}, then R^{3c} is other than Me or CF_3;

or a pharmaceutically acceptable salts or solvates thereof, or solvates of the pharmaceutically acceptable salts.

[0026] In another example~~a further aspect, the present invention~~ 1,2,4-triazolo[1,5-a]pyridine compounds according to Formula I are disclosed that are capable of ~~capable of~~ modulating the activity of JAK *in vivo*.

[0027] In yet another example~~a further aspect~~, the present ~~invention~~disclosure provides pharmaceutical compositions comprising a compound of the ~~invention~~present disclosure, and a pharmaceutical carrier, excipient or diluent. In this example~~aspect of the invention~~, the pharmaceutical composition can comprise one or more of the compounds described herein. Moreover, the compounds of the present ~~invention~~disclosure useful in the pharmaceutical compositions and treatment methods disclosed herein, are all pharmaceutically acceptable as prepared and used.

[0027a] In one aspect, there is provided the use of a compound according to Formula I:



III

wherein

L1 is selected from a single bond, -O-, -N(R^{4a})-, -C(O)-, C[=N(R^{4a})]-, -CON(R^{4a})-, -SO_2N(R^{4a})-, -S(O)$_2$-, -N(R^{4a})SO_2- and -N(R^{4a})CO-; n1 is 0, 1, 2, 3, or 4; and R^{3b} is substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5-10 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, or S, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S;

R^{4a} is H, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 alkoxy;

wherein the substituents for the term "substituted" in the definition of R^{3b}, and R^{4a} are selected from the group consisting of:

halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR'''SO_2R''$, -$SO_2NR''R'''$, -C(O)R'', -C(O)OR'', -OC(O)R'', -NR'''C(O)R'', -C(O)$NR''R'''$, -$NR''R'''$, -$(CR'''R''')_mOR'''$, wherein, each R'' is independently selected from H, C_1-C_8 alkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5-10 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, or S), -$(CH_2)_t$(C_3-C_{10} cycloalkyl), and -$(CH_2)_t$(4-10 membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S), wherein t is an integer from 0 to 4; and

- any alkyl groups present, may themselves be substituted by halo or hydroxy; and
- any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxyl;

each R''' independently represents H or C_1-C_6alkyl; and

provided that

i) when L1 is –O-, -N(R^{4a})-, -CON(R^{4a})-, or -SO_2N(R^{4a})-, and R^{3b} is other than cycloalkyl, aryl or 5-10 membered heteroaryl, then n1 is 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prevention of rheumatoid arthritis, osteoarthritis, allergic airways disease, inflammatory bowel diseases, chronic obstructive pulmonary disorders, asthma, systemic lupus erythematosis, Castleman's disease or mesangial proliferative glomerulonephritis, endotoxin-driven disease states, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and transplantation rejection.

[0028] In another example~~a further aspect of the invention~~, this ~~invention~~disclosure provides a method of treating a mammal susceptible to or afflicted with a condition from among those listed herein, and particularly, such condition as may be associated with aberrant JAK activity, for example diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases,

endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection), which method comprises administering an effective amount of one or more of the pharmaceutical compositions or compounds described herein. Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a particular ~~embodiment~~example the present ~~invention~~disclosure provides a method for treating conditions selected from inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn's disease, colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis, which method comprises administering an effective amount of one or more of the pharmaceutical compositions or compounds described herein.

[0029] In another example~~a further aspect~~, the present ~~invention~~disclosure provides compounds according to Formula I or a pharmaceutically acceptable salt thereof in the treatment and./or prevention of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection) or proliferative diseases.

[0030] In a further example~~aspect~~, the present ~~invention~~disclosure provides a method of treating a mammal susceptible to or afflicted with proliferative disorders in particular cancer, (e.g. solid tumours), leukaemias, multiple myeloma or psoriasis.

[0031] In a further example~~aspect~~, the present ~~invention~~disclosure provides a compound of the ~~invention~~disclosure for use in the treatment or prevention of a condition selected from those listed herein, particularly such conditions as may be associated with aberrant JAK activity such as diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states

contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a specific embodiment, the condition is selected from inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn's disease, colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis.

[0032] In a further exampleaspect, the present inventiondisclosure provides a compound of the invention for use in the treatment or prevention of proliferative disorders, in particular cancer, (e.g. solid tumours), leukaemias, multiple myeloma or psoriasis.

[0033] In yet another examplemethod of treatment aspect, this inventiondisclosure provides a method for treating a mammal susceptible to or afflicted with a condition that is causally related to abnormal JAK activity as described herein, and comprises administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds herein described.

[0034] In a further exampleaspect, the present inventiondisclosure provides a compound of the invention for use in the treatment or prevention of a condition that is causally related to abnormal JAK activity.

[0035] In additional examplesaspects, this inventiondisclosure provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.

[0036] Accordingly, it is a principal object of this inventiondisclosure to provide a novel series of compounds, which can modify the activity of JAK and thus prevent or treat any maladies that may be causally related thereto.

[0037] It is further an object of this inventiondisclosure to provide a series of compounds that can treat or alleviate maladies or symptoms of same, such as cartilage and/or bone degradation and related inflammation, and joint diseases, that may be causally related to the activity of JAK.

[0038] A still further object of this inventiondisclosure is to provide pharmaceutical compositions that may be used in the treatment or prevention of a variety of disease states, including the diseases associated with JAK activity such as diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic

stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a specific ~~embodiment~~example the condition is selected from inflammation, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis or cancers (e.g. solid tumours or leukaemias).

[0039] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0040] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0041] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term "substituted" is to be defined as set out below. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein.

[0042] The articles "a" and "an" may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[0043] 'Acyl' refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. Exemplary 'acyl' groups are $-C(O)H$, $-C(O)$-C_1-C_8 alkyl, $-C(O)$-$(CH_2)_t$(C_6-C_{10} aryl), $-C(O)$-$(CH_2)_t$(5-10 membered heteroaryl), $-C(O)$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and $-C(O)$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0044] 'Substituted Acyl' refers to a radical $-C(O)R^{21}$, wherein R^{21} is independently