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.

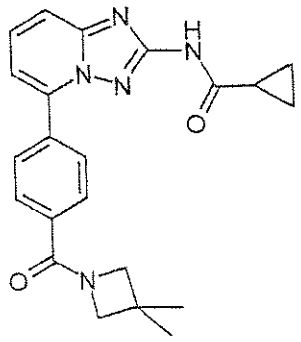
[0015] The current therapies are not satisfactory and therefore there remains a need to identify further compounds that may be of use in the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6. The present invention therefore provides a compound, methods for its manufacture and pharmaceutical compositions comprising the compound of the invention together with a suitable pharmaceutical carrier. In particular, the compound exhibits high potency and selectivityfor JAK1 over other JAK family members in addition to 385 kinase and non-kinase targets. Additionally, data indicates that the compound has a good safety margin. Therefore it is concluded that the present invention offers a novel opportunity for treating JAK1 mediated diseases, in particular inflammatory diseases such as SLE (systemic lupus erythematosus) and RA.

[0016] The present invention also provides for the use of the compound of the invention in the preparation of a medicament for the treatment of these diseases and conditions.

SUMMARY OF THE INVENTION

[0017] The present invention is based on the discovery that inhibitors of JAK, in particular JAK1 are useful for the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6. The present disclosure~~invention~~ also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 by administering the compound of the invention.

[0018] Accordingly, in a first aspect of the invention, a compound of the invention is disclosed having a Formula I:



I

or a pharmaceutically acceptable salt thereof.

[0019] The compound of the invention is a novel inhibitor of JAK that exhibits a high potency and selectivity for JAK1 over other JAK family members and 385 kinase and non-kinase targets as well as showing a good safety margin. The use of a compound with this profile may result in advantages in the treatment of inflammatory diseases, in particular SLE and RA due to a lower incidence of off-target effects.

[0019a] In one aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or pharmaceutically acceptable salt thereof, as defined above.

[0020] In one example~~a further aspect~~, the present disclosure~~invention~~ provides pharmaceutical compositions comprising the compound of the invention, and a pharmaceutical carrier, excipient or diluent. Moreover, the compound of the present disclosure~~invention~~ useful in the pharmaceutical compositions and treatment methods disclosed herein, is pharmaceutically acceptable as prepared and used. In this example~~aspect of the invention~~, the pharmaceutical composition may additionally comprise further active ingredients suitable for use in combination with the compound of the invention.

[0021] In another example ~~further aspect of the invention~~, the present disclosure~~this invention~~ 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 inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6, which method comprises administering a therapeutically effective amount of the compound of the disclosure~~invention~~, or one or more of the pharmaceutical compositions herein described. In another example ~~specific aspect~~, this disclosure~~invention~~ provides a method of treating a mammal susceptible to or afflicted with a condition as may be associated with aberrant JAK1 activity, in particular inflammatory conditions, proliferative diseases and diseases involving impairment of cartilage turnover.

[0021a] In one aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as defined above in the manufacture of a medicament.

[0021b] In another aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, as defined above for use as a medicament.

[0021c] In another aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, as defined above for use in the treatment, prevention or prophylaxis of inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or psoriasis.

[0021d] In another aspect, there is provided the use of a compound, or pharmaceutically acceptable salt thereof, as defined above in the preparation of a medicament for the treatment, prevention or prophylaxis of inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or psoriasis.

[0022] In another example ~~further aspect~~, the present disclosure ~~invention~~ provides the compound of the invention 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 inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6. In a specific example ~~aspect~~, the present disclosure ~~invention~~ provides the compound as described herein ~~of the invention~~ for use in the treatment or

prevention of conditions associated with aberrant JAK1 activity, in particular inflammatory conditions, proliferative diseases and diseases involving impairment of cartilage turnover.

[0023] In yet another example~~method of treatment aspect~~, the present disclosure~~this invention~~ provides a method for treating a mammal susceptible to or afflicted with a condition that is casually related to abnormal JAK activity as described herein, which method comprises administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or the compound of the invention herein described. In a specific embodiment the abnormal JAK activity is abnormal JAK1 activity.

[0024] In another example ~~further aspect~~, the present disclosure~~invention~~ provides the compound as described herein~~of the invention~~ for use in the treatment or prevention of a condition that is casually related to abnormal JAK activity. In a specific embodiment the abnormal JAK activity is abnormal JAK1 activity.

[0025] In additional example~~aspects~~, the present disclosure~~this invention~~ provides methods for synthesizing the compound as described herein~~of the invention~~, with representative synthetic protocols and pathways disclosed later on herein.

[0026] Accordingly, it is a principal object of this disclosure~~invention~~ to provide a compound, which can modify the activity of JAK and thus prevent or treat any conditions that may be causally related thereto. In particular any conditions which may be causally related to the activity of JAK1.

[0027] It is further an object of the present disclosure~~this invention~~ to provide a compound that can treat or alleviate conditions or diseases or symptoms of same, such as inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and diseases associated with hypersecretion of IL6, that may be causally related to the activity of JAK. In particular disease or condition which may be causally related to the activity of JAK1.

[0028] Also disclosed are~~A still further object of this invention 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 inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and diseases associated with hypersecretion of IL6. In particular conditions associated with JAK1 activity.

[0029] 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

[0030] 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.

[0031] 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