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 inhibitors of JAK, may also find utility in the treatment of said diseases.

[0018] 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, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, in particular rheumatoid arthritis.

[0019] Additionally, these conditions are chronic conditions which require long term therapy, and repeated intake of the drug. Long term treatment might be a heavy burden on the patient and the practitioner alike, since the patient might be or become intolerant to the drug, and furthermore high dosage, or high dosage frequency may result in uncomfortable side effects, and /or low patient compliance, where the patient may occasionally, deliberately or accidentally, miss a dose. The impact of non-adherence varies across chronic illnesses, and ranges from minimal to very significant. (Ingersoll *et al.*, 2008 J Behav Med.; 31(3): 213–224).

[0020] Therefore, there is a need to identify more compounds to reinforce the arsenal of the practitioner, and compounds with low frequency dosage regimen to improve the life of the patients.

[0021] In the quest to discover new medicines, criteria are often set to identify the best suitable candidate, thus many compounds are rapidly assessed in an *in vitro* model, and equally rapidly discarded if they do not meet said criteria. *In vitro* studies usually have a higher throughput than *in vivo* studies and greatly help with the decision making process. Thus the *in vitro* model is usually expected to be predictive of the *in vivo* behavior of the drug, and compounds which *prima facie* would not appear to offer a suitable profile *in vitro* are discarded. In this context, the compound according to Formula I when investigated showed *in vitro* profile of low interest, however, *in vivo* studies revealed unexpected properties in humans specifically.

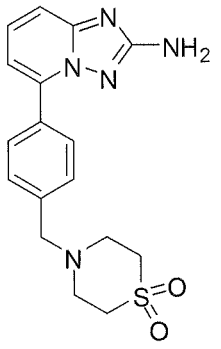
SUMMARY OF THE INVENTION

[0022] The present ~~invention~~ disclosure is based on the discovery that the compound ~~of the invention~~ as described herein according to Formula I may be useful as a medicament. In a particular aspect, the compound ~~of the invention~~ according to Formula I is an inhibitor of JAK, and more particularly JAK1.

[0023] The present ~~invention~~ disclosure also provides methods for the production of the compound ~~of the invention~~ as described herein according to Formula I, pharmaceutical compositions comprising the compound ~~of the invention~~ as described herein according to Formula I and methods for the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases

associated with hypersecretion of IL6 or interferons, in particular rheumatoid arthritis, by administering the compound ~~of the invention~~ as described herein according to Formula I.

[0024] Accordingly, in a first aspect ~~of the invention~~ as described herein, a compound ~~of the invention~~ as described herein is provided for use in medicine having a Formula I:



I

[0025] The compound ~~of the invention~~ according to Formula I, surprisingly, exhibits *in vivo* in human a very different profile from other animal species, which contrasts with *in vitro* predictions. Indeed, *in vivo* it has been demonstrated that in human, the apparent terminal half life of the compound ~~of the invention~~ according to Formula I is significantly longer than in the other animal species by at least 3 fold. This causes accumulation in human resulting in a maintained therapeutic effect over an extended period of time, thereby allowing once daily to once weekly dosing. Thus the compound ~~of the invention~~ according to Formula I may provide advantages including a low frequency dosage regimen and / or increased patient compliance. In particular, the impact of non adherence, if the patient misses a dose, might be reduced.

[0026] In a particular aspect, the compound ~~of the invention~~ according to Formula I is provided for use in the prophylaxis and / or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, in particular rheumatoid arthritis.

[0027] In a further aspect, the present ~~invention~~ disclosure provides pharmaceutical compositions comprising the compound of the invention according to Formula I, and a pharmaceutical carrier, excipient or diluent. In a particular aspect, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compound ~~of the invention~~ according to Formula I. In a more particular aspect, the further therapeutically active ingredient is a compound for the treatment of arthritis. In a most particular aspect, the further therapeutically active ingredient is a compound for the treatment of rheumatoid arthritis.

[0028] Moreover, the compound ~~of the invention~~ according to Formula I, useful in the pharmaceutical compositions and treatment methods disclosed herein, is pharmaceutically acceptable as prepared and used.

[0029] In a further aspect ~~of the invention~~, ~~this invention~~ there is provided~~s~~ use of a therapeutically effective amount of a compound as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for the prophylaxis and/or treatment of a mammal susceptible to or afflicted with a condition selected from inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, more particularly rheumatoid arthritis , wherein said compounds, JAK inhibitor and said pharmaceutical composition exhibit demonstrable activity *in vivo*. Also disclosed is a method of treating a mammal, in particular humans, susceptible to or afflicted with a condition selected from among those listed herein, and particularly inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, more particularly rheumatoid arthritis, which method comprises administering a therapeutically effective amount of the pharmaceutical composition or compound of the invention according to Formula I as described herein.

[0030] The present ~~invention~~ disclosure also provides pharmaceutical compositions comprising the compound ~~of the invention~~ according to Formula I, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, in particular rheumatoid arthritis.

[0031] In additional aspects, this ~~invention~~ present disclosure provides methods for synthesizing the compound ~~of the invention of~~ according to Formula I, with representative synthetic protocols and pathways disclosed later on herein.

[0032] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] **Figure 1:** Shows the rat CIA Clinical Score after treatment with the compounds disclosed herein.

[0034] **Figure 2:** Shows the evolution of ankle diameter in the rat CIA model after treatment with the compounds disclosed herein.

[0035] **Figure 3:** Shows the *in vitro* metabolic profile of the compound according to Formula II

[0036] **Figure 4:** Shows the ratio of exposure (expressed as AUC) for Formula I:Formula II measured on administration of the compound according to Formula II.

[0037] **Figure 5:** Shows the values for the exposure levels of the disclosed compounds after administration of the compound according to Formula II expressed as a multiple of the IC_{50} value.

[0038] **Figure 6:** Shows the combined values for the exposure levels over a 24h period of the compounds according to Formula I and Formula II after administration of the compound according to Formula II expressed as a multiple of the IC_{50} value.

17. The pharmaceutical composition according to any one of claims 8-13, for use in the treatment of inflammatory bowel diseases.

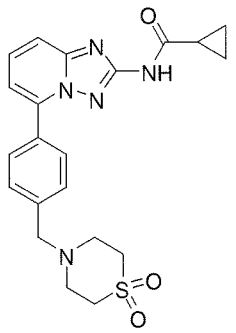
18. The pharmaceutical composition according to any one of claims 8-13, for use in the treatment of psoriasis and/or psoriatic arthritis.

19. ~~A method for the prophylaxis and/or treatment of a mammal susceptible to or afflicted with a condition selected from inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, more particularly rheumatoid arthritis, which method comprises administering~~ Use of a therapeutically effective amount of a compound of claims 1-7, or the pharmaceutical composition of claims 8-13 in the manufacture of a medicament for the prophylaxis and/or treatment of a mammal susceptible to or afflicted with a condition selected from inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, more particularly rheumatoid arthritis , wherein said compounds, JAK inhibitor and said pharmaceutical composition exhibit demonstrable activity *in vivo*.

20. The ~~method~~ use according to claim 19, wherein the said compounds, JAK inhibitor and said pharmaceutical composition are to be administered in combination with one or more additional therapeutic agents.

21. The ~~method~~ use according to claim 20, wherein said additional therapeutic agent is a rheumatoid arthritis treating agent.

22. The ~~method~~ use according to claim 20, wherein the additional therapeutic agent is according to Formula II:



II .

23. The ~~method~~ use according to claim 22, wherein the ratio of Formula I/Formula II is from 1/5 to 1/20.

24. The ~~method~~ use according to claim 22, wherein the ratio of Formula I/Formula II is from 1/5 to 1/10.

25. The ~~method~~ use according to any of claims 19-24, wherein the mammal is a human.