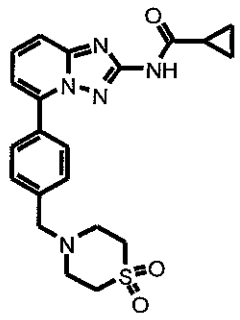
[0012] The compound of the invention, cyclopropanecarboxylic acid {5-[4-(1,1-dioxo-thiomorpholin-4-ylmethyl)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl}-amide (Compound 1), is disclosed in WO2010/149769 (Menet and Smits, 2010) and has the chemical structure shown below:



I

[0013] Compound 1 is a JAK inhibitor, more particularly a JAK1 inhibitor, and was disclosed as being useful 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.

[0014] Compound 1 was previously dosed in clinical testing for a period of 4 weeks in patients who have not previously received biological treatments for RA, where the patients received concomitant methotrexate therapy. Methotrexate is a well-established and trusted treatment for inflammatory conditions and autoimmune diseases (e.g. RA), in particular the ubiquitous nature of methotrexate therapies for these conditions has resulted in authorities and ethical committees for clinical trials being resistant to the use of "pure" placebo arms (i.e. no therapy at all) in randomized clinical trials of new agents tested for the treatment of these conditions (Kaltsonoudis et al.). For that reason, the treatment of RA patient classified as methotrexate non-responders or insufficient responders is usually the first challenge for emerging drugs in this area. Nevertheless, in order to improve patient life condition and compliance, single agent drug treatment are highly desirable. Indeed, single treatment may be beneficial in reducing drug-drug interaction, especially in patients under additional therapies.

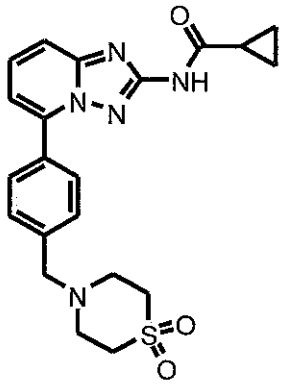
[0015] Furthermore, JAK inhibitors have been reported to have the potential for causing anemia in patients (O'Shea et al., 2013), This unwanted side effect is a known dose-limiting issue for rheumatoid arthritis, and additionally for IBD, would clearly limit the therapeutic window, as patients are already at an increased risk of anemia. Therefore, there is a need for JAK inhibitors for use in the treatment of inflammatory conditions which have a reduced risk or no risk of anaemia.

SUMMARY OF THE INVENTION

[0016] The present disclosure provides the compound of the disclosure according to Formula I for use in the treatment of inflammatory conditions, in particular for use in the treatment of rheumatoid arthritis or Crohn's disease when dosed alone or in combination, orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d.

[0017] The present disclosure also provides methods treatment of inflammatory conditions by administering the compound of the disclosure orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d.

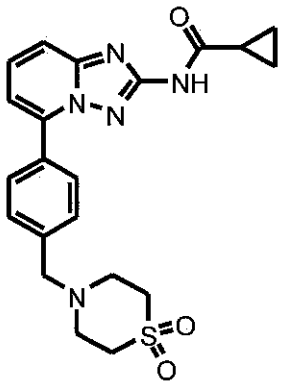
[0018] Accordingly, disclosed is the compound of the disclosure having according to Formula I shown below:



I

is provided for use in the treatment of inflammatory conditions where the compound of the disclosure is dosed orally at a dose of between 25mg to 400 mg, administered once or twice a day. In particular, the compound of the disclosure is dosed orally at a dose of between 100 mg to 250 mg. More particularly, at a dose is selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d.

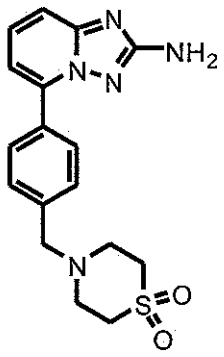
[0018a] In one aspect, the present invention provides a compound according to Formula I:



I

or a pharmaceutically acceptable salt thereof, or a solvate or the salt of a solvate thereof, or an active metabolite thereof for use in the treatment of inflammatory conditions.

[0018b] In another aspect, the present invention provides a compound according to Formula II:



II

or a pharmaceutically acceptable salt thereof, or a solvate or the salt of a solvate thereof, for use in the treatment of inflammatory conditions

[0019] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of rheumatoid arthritis or IBD (e.g. Crohn's disease or ulcerative colitis).

[0020] In a particular example the patient does not take methotrexate concomitantly with the administration of the compound of the disclosure.

[0021] In a specific example, the patient does not receive any other treatment for rheumatoid arthritis or IBD (e.g. Crohn's disease or ulcerative colitis) concomitantly with the administration of the compound of the disclosure.

[0022] In a specific example, the compound of the disclosure is dosed as the sole treatment agent.

[0023] In an alternative example the patient takes methotrexate concomitantly with the administration of compound of the disclosure, in particular between 5-25 mg once per week of methotrexate, more particularly between 10-25 mg once per week of methotrexate, over a period greater than 4 weeks.

[0024] In an alternative example the patient takes methotrexate concomitantly with the administration of compound of the disclosure, in particular between 5-25 mg once per week of methotrexate, more particularly between 10-25 mg once per week of methotrexate, over a period greater than 8, 12, 16, or 20 weeks.

[0025] In an alternative example the patient takes methotrexate concomitantly with the administration of compound of the disclosure, in particular between 5-25 mg once per week of methotrexate, more particularly between 10-25 mg once per week of methotrexate, over a period of at least 24 weeks.

[0026] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose

selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d. for at least 4 weeks. In particular the compound of the disclosure is dosed for at least 8 weeks. In particular the compound of the disclosure is dosed for at least 10 weeks. In particular the compound of the disclosure is dosed for at least 12 weeks. In particular the compound of the disclosure is dosed for at least 16 weeks. In particular the compound of the disclosure is dosed for at least 20 weeks. In particular the compound of the disclosure is dosed for at least 24 weeks.

[0027] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where an ACR20 response is seen in at least 50% of patients.

[0028] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where an ACR50 response is seen in at least 30% of patients.

[0029] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where an ACR70 response is seen in at least 10% of patients.

[0030] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where an ACR70 response is seen in at least 20% of patients. Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where an ACR70 response is seen in at least 20% of patients after 20 weeks.

[0031] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where a reduction in the DAS28(CRP) score of at least 1.8 is seen after 12 weeks of treatment.

[0032] Also disclosed is the compound of the disclosure for use in the treatment of chronic inflammatory conditions, wherein the compound of the disclosure is dosed orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d., where a reduction in the DAS28(CRP) score of at least 2.0 is seen after 24 weeks of treatment.

[0033] Also disclosed is the compound of the disclosure for use in the treatment of Crohn's disease, wherein the compound is dosed at 200 mg q.d., and wherein a reduction in CDAI score of at least

70, at least 80, at least 90, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 200 or at least 250 is seen after 10 weeks treatment. In a more particular example, the compound is dosed at 200 mg q.d., and the patient achieves clinical remission (CDAI score < 150) after 2 weeks, after 4 weeks, after 6 weeks, or after 10 weeks . In another particular example, the compound is dosed at 200 mg q.d., and the patient achieves clinical remission after 10 weeks (CDAI score < 150).

[0034] Also disclosed is the compound of the disclosure for use in the treatment of Crohn's disease, wherein the compound is dosed at 200 mg q.d., and wherein prior to treatment, the Crohn's disease patient shows a CDAI score of at least 220 points, at least 250 points, at least 300 points, at least 350 points, or at least 400 points,. In a particular example, prior to treatment, the Crohn's disease patient shows a CDAI score of at least 250 points, at least 300 points or at least 350 points. In a more particular example, prior to treatment, the Crohn's disease patient shows a CDAI score of at least 250 points, at least 260 points, at least 270 points, at least 280 points, at least 290 points, or at least 300 points.

[0035] Also disclosed is a compound of the disclosure for use in the prophylaxis and/or treatment of IBD, wherein the patient is a TNF naïve patient. In a particular example, the present disclosure provides a compound of the disclosure for use in the prophylaxis and/or treatment of Crohn's disease, wherein the patient is a TNF naïve patient.

[0036] Also disclosed is a compound of the disclosure for use in the prophylaxis and/or treatment of IBD, wherein the patient is a TNF experienced patient. Also disclosed is a compound of the disclosure for use in the prophylaxis and/or treatment of Crohn's disease, wherein the patient is a TNF experienced patient. In a further more particular example, the patient is a TNF experienced patient, wherein the anti-TNF therapy is selected from infliximab, adalimumab, golimumab, certolizumab and certolizumab pegol.

[0037] In another example, the patient has a serum CRP level prior to starting treatment with the compound of the disclosure of 10 mg / L or higher.

[0038] In another example, prior to and/or concomitantly with treatment with the compound of the disclosure, the patient is administered corticosteroids. In particular, the corticosteroid is selected from hydrocortisone, methylprednisolone, prednisone, prednisolone, or budesonide. In a more particular example, the patient is concomitantly receiving and/or has received a daily corticosteroid dose of 20 to 30 mg/day prednisolone/equivalent. In a most particular example, the patient is receiving a daily corticosteroid dose of 20, 21, 22, 23, 24, or 25 mg/day prednisolone/equivalent.

[0039] In another example, prior and/or concomitantly to treatment with the compound of the disclosure, the patient is receiving treatment using 5-aminosalicylates. In particular, the 5-aminosalicylate is selected from sulfasalazine and mesalamine.

[0040] Also disclosed is a method of treating a patient afflicted with a condition selected from among those listed herein which method comprises administering the compound of the disclosure orally at a dose selected from 25 mg twice per day (b.i.d.), 50 mg once a day (q.d.), 50 mg b.i.d., 100 mg q.d., 100 mg b.i.d., and 200 mg q.d.

[0041] In additional example, this disclosure discloses methods for synthesizing the compound of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0042] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0043] It will be appreciated that the compound of the disclosure may be metabolized to yield biologically active metabolites.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **FIGURE 1** shows the percentage of the patient population achieving an ACR20 response at the 1, 2, 4, 8 and 12 week treatment time points in Study 1. The y-axis is the percentage of patients meeting the ACR20 criteria. Figure 1A shows: placebo (pale solid line), 50 mg q.d. (dotted line), 100 mg q.d. (dashed line) or 200 mg q.d. (dark solid line). Figure 1B shows: placebo (pale solid line), 25 mg b.i.d. (dotted line), 50 mg b.i.d. (dashed line) or 100 mg b.i.d. (dark solid line). The results shown in the figures are calculated using the non-responder imputation (NRI), which assigns a value of nonresponse to missing data points, i.e. any patient who drops out is assumed to be a non-responder (NR).

[0045] **FIGURE 2** shows the percentage of the patient population achieving an ACR50 response at the 1, 2, 4, 8 and 12 week treatment time points in Study 1. The y-axis is the percentage of patients meeting the ACR50 criteria. Figure 2A shows: placebo (pale solid line), 50 mg q.d. (dotted line), 100 mg q.d. (dashed line) or 200 mg q.d. (dark solid line). Figure 2B shows: placebo (pale solid line), 25 mg b.i.d. (dotted line), 50 mg b.i.d. (dashed line) or 100 mg b.i.d. (dark solid line). The results shown in the figures are calculated using the non-responder imputation (NRI), which assigns a value of nonresponse to missing data points, i.e. any patient who drops out is assumed to be a non-responder (NR).

[0046] **FIGURE 3** shows the percentage of the patient population achieving an ACR70 response at the 1, 2, 4, 8 and 12 week treatment time points in patients in Study 1. The y-axis is the percentage of patients meeting the ACR70 criteria. Figure 3A shows: placebo (pale solid line), 50 mg q.d. (dotted line), 100 mg q.d. (dashed line) or 200 mg q.d. (dark solid line). Figure 3B shows: placebo (pale solid line), 25 mg b.i.d. (dotted line), 50 mg b.i.d. (dashed line) or 100 mg b.i.d. (dark solid line). The results shown in the figures are calculated using the non-responder imputation (NRI), which assigns a value of nonresponse to missing data points, i.e. any patient who drops out is assumed to be a non-responder (NR).

[0047] **FIGURE 4** shows the decrease in the DAS28(CRP) score in the patient population at the 1, 2, 4, 8 and 12 week time points for each dose in Study 1. Figure 4A shows placebo (pale solid line), 50 mg q.d. (dotted line), 100 mg q.d. (dashed line) or 200 mg q.d. (dark solid line). Figure 4B shows: placebo (pale solid line), 25 mg b.i.d. (dotted line), 50 mg b.i.d. (dashed line) or 100 mg b.i.d. (dark solid line). The results shown in the figures are calculated using Last-Observation-Carried-Forward (LOCF), which handles missing data by assigning the value recorded at the patient's last visit to all subsequent missed visits.

[0048] **FIGURE 5** shows the decrease in the serum CRP level in mg/L in the patient population at the 1, 2, 4, 8 and 12 week time points for each dose in Study 1. Figure 5A shows placebo (pale solid line),