[0022] The identification and development of new agents for the treatment of cardiovascular disorders and/or dyslipidemia would be highly desirable, both for patients suffering from inflammatory disorders, *e.g.* RA patients, and non-inflamed patients alike. In particular, there is a need for anti-inflammatory therapies which not only restore abnormal lipid profile levels in patients to normal recommended values as defined herein, but which do so with a preferential increase in [HDL], relative to [LDL].

SUMMARY OF THE INVENTION

[0023] The present disclosure provides the compound of the disclosure according to Formula I (Compound 1) for use in the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia. In particular, the compound of the disclosure may act as an inhibitor of JAK, and more particularly of JAK1.

[0024] Furthermore, the present disclosure provides pharmaceutical compositions comprising the compound according to Formula I (Compound 1) for use in the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia.

[0025] The present disclosure also provides methods for the production of these pharmaceutical compositions of the disclosure and methods for the treatment and/or prophylaxis of cardiovascular disorders by administering the pharmaceutical compositions of the disclosure.

[0026] When Compound 1 was administered orally in humans, an unexpected change in the lipid profile was observed.

[0027] Without being limited by theory, the inventors believe that this effect could be associated with Compound 1's particular kinase selectivity profile, particular towards JAK1, since the same effect is not shown by other JAK inhibitors that have been tested.

[0028] For example, in the controlled clinical trials of Tofacitinib, a JAK inhibitor, dose-related elevations in lipid parameters, including [total cholesterol], [LDL], and [HDL], were observed. In particular the following changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials were as follows: mean [LDL] increased by 15% in the 5 mg twice daily arm and 19% in the 10 mg twice daily arm; mean [HDL] increased by 10% in the 5 mg twice daily arm and 12% in the 10 mg twice daily arm, whereas mean [LDL]/[HDL] ratios were essentially unchanged in patients, (FDA Application No. (NDA) 203214, summary review 203214Orig1s000), thus raising initial lipid levels, but with a unfavorable [HDL] vs [LDL] ratio.

[0029] In contrast, whereas Compound 1 raised the low [total cholesterol] levels, an unexpected disproportionate rise in blood of [HDL] vs [LDL] was observed. In particular, [HDL] levels of 5-23% compared to initial levels were seen. Moreover, this rise in [HDL] was substantially higher than the corresponding increases in [LDL] levels. In particular between 1.1 and 4 fold higher increases in [HDL] vs. [LDL] were seen.

[0030] Moreover, it has been coined in that the [total cholesterol]/[HDL] ratio otherwise known as the 'atherogenic index', has a great predictive capacity of cardiovascular risks (Millán et al., 2009). Accordingly, for example, in men a [total cholesterol]/[HDL] ratio of 1.68-4.21 resulted in a

cardiovascular risk increase of 11-16%, a [total cholesterol]/[HDL] ratio of 4.22-5.53 resulted in a cardiovascular risk increase of 19-29%, and a [total cholesterol]/[HDL] ratio of 5.54-18.1 resulted in a cardiovascular risk increase of 26-33% (Nam et al., 2006).

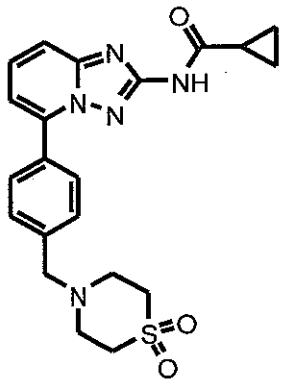
[0031] Typically, in a recent treatment study with Tofacitinib, a JAK inhibitor for 6 weeks at a dose of 10 mg bid in RA patient, the atherogenic index was unchanged before and after treatment at about 3.5 (Charles-Schoeman et al., 2015) thus leaving the patient at an increased cardiovascular risk before and after treatment. In contrast, upon administration of Compound 1 at doses ranging from 50 mg to 200 mg (once or twice daily) for a period of at least 4 weeks resulted in a drop of the atherogenic index, thereby reducing the initial cardiovascular risk.

[0032] Furthermore, this effect was sustained over at least 12 weeks, and at least 24 weeks and were observed over a dose range of 50-200 mg administered either twice daily (b.i.d) or once a day (q.d.).

[0033] Additionally, this effect was seen both in healthy volunteers, and patients suffering from inflammatory diseases (for example RA and Crohn's disease).

[0034] Therefore Compound 1 would be particularly advantageous in preventing and/or treating cardiovascular disorder, and the object of the present disclosure is Compound 1 for use in the prophylaxis and/or treatment of cardiovascular disorder and/or dyslipidemia.

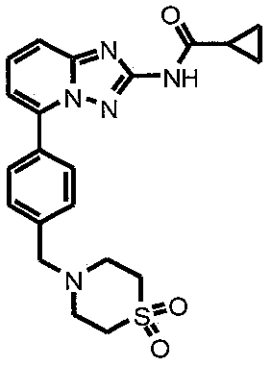
[0035] Accordingly, disclosed is the compound of the disclosure having a Formula (I):



I

is provided for use is the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia.

[0035a] 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 prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia.

[0036] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of chronic cardiovascular disorders. In a more particular example, the cardiovascular disorder is atherosclerosis.

[0037] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of chronic dyslipidemia. In a more particular example, the cardiovascular disorder is hypolipidemia.

[0038] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of cardiovascular disorders in patients not suffering from RA as measured by the DAS28(CRP) score method (Wells et al., 2008), wherein the DAS28(CRP) value is less than 2.6.

[0039] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of cardiovascular disorders in RA patients, wherein the treatment extends for longer than 4 weeks.

[0040] Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of cardiovascular disorders in IBD patients. Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of cardiovascular disorders in ulcerative colitis and/or Crohn's disease patients. Also disclosed is the compound of the disclosure for use in the prophylaxis and/or treatment of cardiovascular disease in Crohn's disease patients.

[0041] Also disclosed are pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in the prophylaxis and/or treatment of cardiovascular disorders. In a more particular example, the cardiovascular disorder is atherosclerosis.

[0041a] In another aspect, the present invention provides a pharmaceutical composition for use in the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia, comprising the compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0042] The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in the prophylaxis and/or treatment of dyslipidemia. In a more particular example, the cardiovascular disorder is hypolipidemia.

[0043] . In a further particular example, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In a more particular example, the further therapeutically active ingredient is an agent for the treatment of cardiovascular disorders.

[0044] In a further particular example, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In a more particular example, the further therapeutically active ingredient is an agent for the treatment of dyslipidemia.

[0045] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0046] Also disclosed is a method for the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia in a mammal in need thereof, in particular humans, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0047] Also disclosed is a method of decreasing the risk of cardiovascular risk in a mammal, in particular humans, which method comprises

administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0048] Also disclosed is a method of increasing [HDL] blood levels in in a mammal in need thereof, in particular humans, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein. In a particular example, the [HDL] compared to prior to the treatment level is increased by at least 5%, at least 10%, at least 15%, at least 20%, and/or at least 23%.

[0049] Also disclosed is a method of decreasing the atherogenic index in a mammal in need thereof, in particular humans, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein. In a particular example, the atherogenic index compared to prior to the treatment level is decreased by at least 0.2, by at least 0.3, and/or at least 0.35.

[0049a] In yet another aspect, the present invention provides use of a dose of the compound according to Formula I, or a pharmaceutically acceptable salt thereof comprised between 25 mg and 400 mg in the manufacture of a medicament for the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia, wherein the compound is to be administered to an individual, wherein the determination of the dose comprising the steps of:

- measuring the DAS28(CRP) levels of an individual by performing a 28 tender and swollen joint count, CRP measurement from blood analysis, and a general health assessment on a visual analog scale,
- comparing said DAS28(CRP) level to the disease scoring index wherein a score below 2.6 is indicative of remission , a score between 2.6 and 3.2 is indicative of low disease activity, a score between 3.2 and 5.1 is indicative of moderate disease activity, and a score above 5.1 is linked to high disease activity

[0050] Also disclosed are methods for synthesizing the compounds of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0051] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0052] It will be appreciated that compounds of the disclosure may be metabolized to yield biologically active metabolites.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Shows the mean percentage change in [Total Cholesterol], [HDL] and [LDL] *vs* baseline in Study 3 in Japanese and Caucasian healthy volunteers after 10 days treatment with Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] at 200 mg/day.

Figure 2. Shows the mean percentage change in [Total Cholesterol], [HDL] and [LDL] *vs* baseline in Study 4 in RA patients upon administration of Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] after 4 weeks treatment of varying doses (30 mg, 75 mg, 150 mg and 300 mg) once a day.

Figure 3. Shows the mean percentage change in [Total Cholesterol], [HDL] and [LDL] vs baseline in Study 1 in RA patients upon administration of Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] after 12 weeks treatment of varying doses 25 mg b.i.d., 50 mg b.i.d., 50 mg q.d. 100 mg b.i.d., 100 mg q.d., 200 mg q.d. vs placebo.

Figure 4. Shows the mean percentage change *vs* baseline in [LDL] level in Study 1 in RA patients upon administration of Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] after 12 weeks treatment of varying doses 25 mg b.i.d.(2x25 mg, asterisk), 50 mg b.i.d. (2x50 mg, filled circles), 50 mg q.d. (50 mg, filled

squares), 100 mg b.i.d. (2x100mg, upward crosses), 100 mg q.d. (100mg, filled triangles), 200 mg q.d. (200mg, tilted crosses), vs placebo (filled diamonds).

Figure 5. Shows the mean percentage change *vs* baseline in [HDL] level in Study 1 in RA patients upon administration of Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] after 12 weeks treatment of varying doses 25 mg b.i.d.(2x25mg, asterisk), 50 mg b.i.d. (2x50mg, filled circles), 50 mg q.d. (50 mg, filled squares), 100 mg b.i.d. (2x100mg, upward crosses), 100 mg q.d. (100mg, filled triangles), 200 mg q.d. (200mg, tilted crosses), vs placebo (filled diamonds).

Figure 6. Shows the mean percentage change *vs* baseline in atherogenic index in Study 1 in RA patients upon administration of Compound 1 (dosed as [Compound 1:HCl:$3H_2O$] after 12 weeks treatment of varying doses 25 mg b.i.d.(2x25mg, asterisk), 50 mg b.i.d. (2x50mg, filled circles), 50 mg q.d. (50 mg, filled squares), 100 mg b.i.d. (2x100mg, upward crosses), 100 mg q.d. (100mg, filled triangles), 200 mg q.d. (200mg, tilted crosses), vs placebo (filled diamonds).

11) A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 1, 2, 3, or 4, or a pharmaceutical composition for use according to claim 6 or 7 in a clinical non RA-afflicted patient, wherein the non RA-afflicted condition is measured by the DAS28(CRP) score, wherein the DAS28(CRP) score is less than 2.6.

12) A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 1, 2, 3, or 4, or a pharmaceutical composition for use according to claim 6 or 7 in a clinical non RA-afflicted patient, wherein the non RA-afflicted condition is measured by the DAS28(CRP) score, and having a CRP level greater than 3 mg/L.

13) A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 1, 2, 3, or 4, or a pharmaceutical composition for use according to claim 6 or 7 in a clinical RA-afflicted patient, wherein the compound of the invention or pharmaceutical compositions comprising a compound of the invention is administered at least once a week over a period of greater than 4 weeks.

14) A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 1, 2, 3, or 4, or a pharmaceutical composition for use according to claim 6 or 7 in a clinical RA-afflicted patient, wherein the clinical RA-afflicted patient condition is measured by the DAS28(CRP) score.

15) A compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition for use according to claim 14, wherein the DAS28(CRP) score is greater than 3.2.

16) A compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition for use according to any one of claims 1-15, wherein said compound, or pharmaceutically acceptable salt thereof is administered at a dose of 100 mg twice a day.

17) A compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition for use according to any one of claims 1-15, wherein said compound, or pharmaceutically acceptable salt thereof is administered at a dose of 200 mg once a day.

18) Use of a dose of the compound according to Formula I, or a pharmaceutically acceptable salt thereof comprised between 25 mg and 400 mg in the manufacture of a medicament for the prophylaxis and/or treatment of cardiovascular disorders and/or dyslipidemia, wherein the compound is to be administered to an individual, wherein the determination of the dose comprising the steps of:

- measuring the DAS28(CRP) levels of an individual by performing a 28 tender and swollen joint count, CRP measurement from blood analysis, and a general health assessment on a visual analog scale,

- comparing said DAS28(CRP) level to the disease scoring index wherein a score below 2.6 is indicative of remission , a score between 2.6 and 3.2 is indicative of low disease activity, a score between 3.2 and 5.1 is indicative of moderate disease activity, and a score above 5.1 is linked to high disease activity.

19) The compound or a pharmaceutically acceptable salt thereof, according to claim 5 or the pharmaceutical composition for use according to claim 7, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of cardiovascular disease.

20) The compound or a pharmaceutically acceptable salt thereof, according to claim 5 or the pharmaceutical composition for use according to claim 7, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of atherosclerosis.