

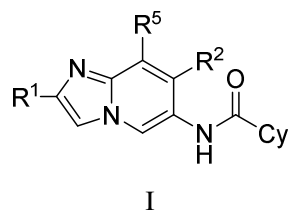
a crucial element when developing new medicines, and therefore, it would be desirable to develop compounds that are able to selectively modulate a signaling pathway without affecting others, in particular compounds able to selectively modulate IL-1 response, without affecting TNF α signaling pathways.

[0011] The current therapies are not satisfactory and therefore there remains a need to identify further compounds with reduced off-target related side effects that may be of use in the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases and/or proliferative diseases.

SUMMARY

[0012] The present disclosure relates to compounds that may be useful in the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases. In particular, the compounds of the disclosure may inhibit Interleukin-1 Receptor Associated Kinases (IRAKs), a family of kinases that are involved in inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases, and more particularly IRAK-4. The present disclosure also provides methods for the production of the compounds of the disclosure, pharmaceutical compositions comprising the compounds of the disclosure, methods for the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, fibrosis and/or proliferative diseases by administering the compound of the disclosure.

[0012a] In one aspect, the present disclosure refers to a compound according to Formula I:



wherein

R¹ is C₂₋₆ alkyl substituted with one or more independently selected -OH, -CN, C₁₋₄ alkoxy, halo, or -S(=O)₂-C₁₋₄ alkyl;

R² is

- a) C₁₋₄ alkoxy which alkoxy is unsubstituted or substituted with one or more independently selected halo or -OH,
- b) -O-C₃₋₄ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo or -OH, or
- c) -C(=O)NR^{3a}R^{3b};

Cy is 6 membered heteroaryl, comprising 1 or 2 N atoms, substituted with one or two independently selected R⁴ substituents;

Each R^{3a} and R^{3b} is independently selected from

- a) H,

- b) C₁₋₄ alkyl, which alkyl is unsubstituted or substituted with one or more independently selected halo, -OH, -CN, C₁₋₄ alkoxy, or C₃₋₇ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo,
- c) C₃₋₆ cycloalkyl which cycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo, or
- d) 4-6 membered heterocycloalkyl comprising one or two independently selected N, S, or O atoms, which heterocycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

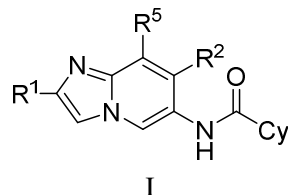
R^{3a} and R^{3b} together with N atom to which they are attached may form a 4-6 membered monocyclic heterocycloalkyl;

Each R⁴ is independently

- a) oxo,
- b) -OH,
- c) -CN,
- d) halo
- e) C₁₋₄ alkyl unsubstituted or substituted with one or more independently selected halo, -OH, or -CN,
- f) C₁₋₄ alkoxy unsubstituted or substituted with one or more independently selected halo, -OH, or -CN, or
- g) C₃₋₇ cycloalkyl unsubstituted or substituted with one or more independently selected halo, -OH or -CN; and

R⁵ is selected from H, halo, -CH₃ or -CF₃;

[0013] or a pharmaceutically acceptable salt thereof, or a solvate or the salt of the solvate thereof, or a metabolite thereof. Accordingly, in a first example, the compounds of the disclosure are provided having a Formula I:



wherein

R¹ is C₂₋₆ alkyl substituted with one or more independently selected -OH, -CN, C₁₋₄ alkoxy, halo, or -S(=O)₂-C₁₋₄ alkyl;

R² is

- a) C₁₋₄ alkoxy which alkoxy is unsubstituted or substituted with one or more independently selected halo or -OH,
- b) -O-C₃₋₄ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo or -OH, or
- c) -C(=O)NR^{3a}R^{3b};

Cy is 6 membered heteroaryl, comprising 1 or 2 N atoms, substituted with one or two independently selected R⁴ substituents;

Each R^{3a} and R^{3b} is independently selected from

- a) H,
- b) C₁₋₄ alkyl, which alkyl is unsubstituted or substituted with one or more independently selected halo, -OH, -CN, C₁₋₄ alkoxy, or C₃₋₇ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo,

- c) C₃₋₆ cycloalkyl which cycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo, or
- d) 4-6 membered heterocycloalkyl comprising one or two independently selected N, S, or O atoms, which heterocycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

R^{3a} and R^{3b} together with N atom to which they are attached may form a 4-6 membered monocyclic heterocycloalkyl;

Each R⁴ is independently

- a) oxo,
- b) -OH,
- c) -CN,
- d) halo,
- e) C₁₋₄ alkyl unsubstituted or substituted with one or more independently selected halo, -OH, or -CN,
- f) C₁₋₄ alkoxy unsubstituted or substituted with one or more independently selected halo, -OH, or -CN, or
- g) C₃₋₇ cycloalkyl unsubstituted or substituted with one or more independently selected halo, -OH or -CN; and

R⁵ is selected from H, halo, -CH₃ or -CF₃.

[0014] In one example, the compounds of the disclosure are provided for use in the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases. In a particular example, the compounds of the disclosure may inhibit the IRAK kinase family members, and more particularly IRAK-4.

[0015] In a further example, the compounds of the disclosure may exhibit good metabolic stability, and good half-life, which may result in lower dosage regimen. In a particular example, the compounds of the disclosure show good stability in hepatocytes, which may result in low hepatic clearance.

[0016] In yet another example, the compounds of the disclosure may show improved solubility, in particular thermodynamic solubility, which may result in improved manufacturability.

[0017] In yet a further example, the compounds of the disclosure may show selectivity towards IRAK-4, which may result in improved safety and lower off-target related side effects.

[0018] In a further aspect, the present disclosure provides pharmaceutical compositions comprising a compound of the disclosure, and a pharmaceutical carrier, excipient or diluent. In a 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 prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases.

[0019] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0020] In a further example of the disclosure, this disclosure provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0020a] In another aspect, the present disclosure refers to a compound or pharmaceutically acceptable salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in medicine.

[0020b] In another aspect, the present disclosure refers to a use of the compound or pharmaceutically acceptable salt as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases.

[0021] The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular example, the pharmaceutical composition is for use in the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases.

[0022] In additional examples, this disclosure provides methods for synthesizing the compounds of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0023] 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

[0024] 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.

[0025] 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.

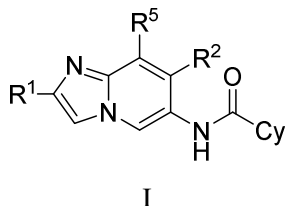
[0026] The articles ‘a’ and ‘an’ may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example ‘an analogue’ means one analogue or more than one analogue.

[0027] ‘Alkyl’ means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl (-CH₃), ethyl (-CH₂-CH₃), n-propyl (-CH₂-CH₂-CH₃), isopropyl (-CH(CH₃)₂), n-butyl (-CH₂-CH₂-CH₂-CH₃), tert-butyl (-CH₂-C(CH₃)₃), sec-butyl (-CH(CH₃)-CH₂-CH₃), n-pentyl (-CH₂-CH₂-CH₂-CH₂-CH₃), n-hexyl (-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃), and 1,2-dimethylbutyl (-CHCH₃)-C(CH₃)H-CH₂-CH₃). Particular alkyl groups have between 1 and 4 carbon atoms.

[0028] ‘Alkenyl’ refers to monovalent olefinically (unsaturated) hydrocarbon groups with the number of carbon atoms specified. Particular alkenyl has 2 to 8 carbon atoms, and more particularly, from 2 to 6

CLAIMS

1. A compound according to Formula I:



wherein

R¹ is C₂₋₆ alkyl substituted with one or more independently selected -OH, -CN, C₁₋₄ alkoxy, halo, or -S(=O)₂-C₁₋₄ alkyl;

R² is

- a) C₁₋₄ alkoxy which alkoxy is unsubstituted or substituted with one or more independently selected halo or -OH,
- b) -O-C₃₋₄ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo or -OH, or
- c) -C(=O)NR^{3a}R^{3b};

Cy is 6 membered heteroaryl, comprising 1 or 2 N atoms, substituted with one or two independently selected R⁴ substituents;

Each R^{3a} and R^{3b} is independently selected from

- a) H,
- b) C₁₋₄ alkyl, which alkyl is unsubstituted or substituted with one or more independently selected halo, -OH, -CN, C₁₋₄ alkoxy, or C₃₋₇ cycloalkyl, which cycloalkyl is unsubstituted or substituted with one or more independently selected halo,
- c) C₃₋₆ cycloalkyl which cycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo, or
- d) 4-6 membered heterocycloalkyl comprising one or two independently selected N, S, or O atoms, which heterocycloalkyl is unsubstituted or substituted with one or more independently selected oxo, -OH, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

R^{3a} and R^{3b} together with N atom to which they are attached may form a 4-6 membered monocyclic heterocycloalkyl;

Each R⁴ is independently

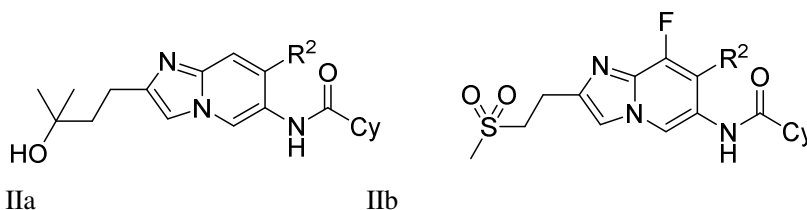
- a) oxo,
 - b) -OH,
 - c) -CN,
 - d) halo
 - e) C₁₋₄ alkyl unsubstituted or substituted with one or more independently selected halo, -OH, or -CN,
 - f) C₁₋₄ alkoxy unsubstituted or substituted with one or more independently selected halo, -OH, or -CN,
- or

- g) C₃₋₇ cycloalkyl unsubstituted or substituted with one or more independently selected halo, -OH or -CN; and

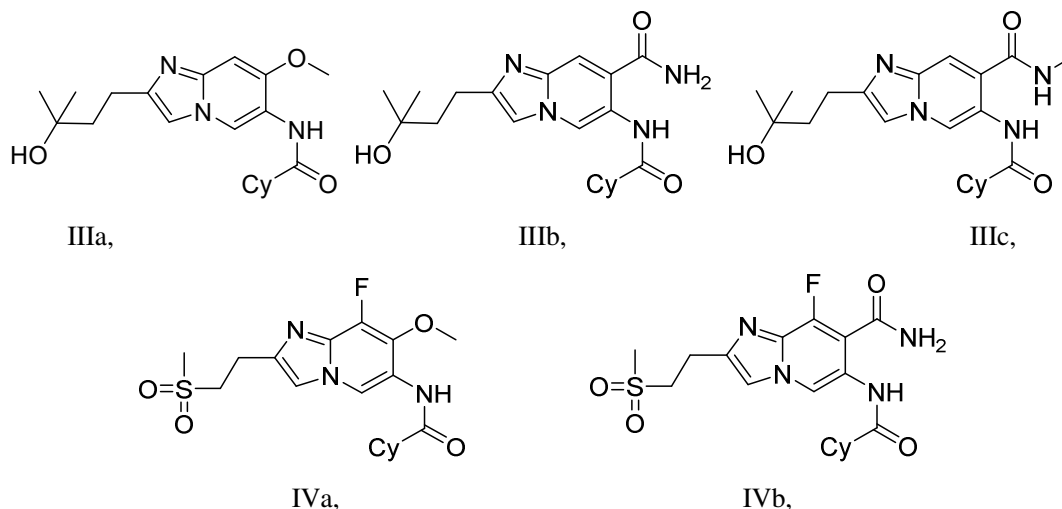
R⁵ is selected from H, halo, -CH₃ or -CF₃;

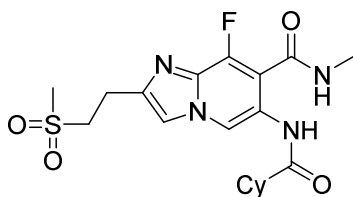
or a pharmaceutically acceptable salt thereof, or a solvate or the salt of the solvate thereof, or a metabolite thereof.

2. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein R¹ is C₂₋₆ alkyl substituted with one or more independently selected -OH, -CN, -OCH₃, F, Cl, or -S(=O)₂CH₃.
3. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein R¹ is -CH₂-CH₂-C(CH₃)₂-OH or -CH₂-CH₂-S(=O)₂CH₃.
4. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula IIa or IIb:

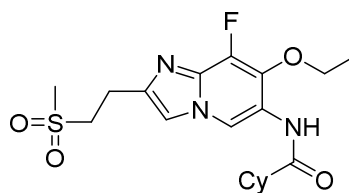


5. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein R² is -OCH₃, or -OCH₂CH₃, each of which is unsubstituted or substituted with one or more independently selected halo or -OH.
6. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein R² is -C(=O)NR^{3a}R^{3b}.
7. The compound or pharmaceutically acceptable salt thereof according to claim 6, wherein R^{3a} is H, -CH₃, -CH₂-CH₃, or -CH(CH₃)₂.
8. The compound or pharmaceutically acceptable salt thereof according to claim 6 or 7, wherein R^{3b} is H, -CH₃, -CH₂-CH₃, or -CH(CH₃)₂.
9. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula IIIa, IIIb, IIIc, IVa, IVb, IVc or IVd:





IVc,



IVd

10. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein Cy is pyridinyl, or pyrazinyl, each of which is substituted with one or two independently selected R⁴ substituents.
11. The compound or pharmaceutically acceptable salt thereof according to claim 10, wherein each R⁴ is independently selected from oxo, -OH, -CN, F, Cl, -CH₃, -CH₂-CH₃, -CH(CH₃)₂, -CF₃, -CHF₃, -CH₂CF₃, -CH₂CN, -CH₂OH, -CH₂CH₂-CN, -O-CH₂-CH₃, cyclopropyl, cyclobutyl, cyclopropyl substituted with one or two independently selected F, or -CN, cyclobutyl substituted with one or two independently selected F, -OH, or -CN.
12. A pharmaceutical composition comprising a compound according to any one of claims 1-11, and a pharmaceutically acceptable carrier thereof.
13. The pharmaceutical composition according to claim 12, further comprising a further therapeutic agent.
14. A compound or pharmaceutically acceptable salt according to claims 1-11, or a pharmaceutical composition according to claims 12 or 13, for use in medicine.
15. Use of the compound or pharmaceutically acceptable salt according to claims 1-11, or a pharmaceutical composition according to claims 12 or 13, in the manufacture of a medicament for the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, pain, fibrosis and/or proliferative diseases.