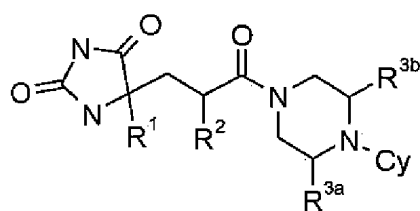


SUMMARY OF THE INVENTION

[0021] The present invention is based on the identification of novel hydantoin compounds that may be useful for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular aspect, the compounds of the invention are inhibitors of ADAMTS-5. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis by administering the compounds of the invention.

[0022] Accordingly, in a first aspect of the invention, the present invention provides a compound according to Formula (I):



I

wherein

R¹ is:

- H,
- C₁₋₄ alkyl optionally substituted with one or more independently selected R⁴ groups,
- C₃₋₇ monocyclic cycloalkyl optionally substituted with one or more independently selected R⁴ groups,
- 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C₁₋₄ alkyl, –C(=O)C₁₋₄ alkyl, or –C(=O)OC₁₋₄ alkyl,
- phenyl optionally substituted with one or more independently selected R⁵ groups,
- phenyl fused to a 5-6 membered monocyclic heterocycloalkyl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, which heterocycloalkyl is optionally substituted with one or more =O, or
- 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R⁵ groups;

R² is independently selected from:

- H,
- OH,
- C₁₋₄ alkoxy, and

- C₁₋₄ alkyl optionally substituted with one or more independently selected halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d},
- C₁₋₄ alkoxy optionally substituted with one -NR^{9e}R^{9f}, or
- S(=O)₂C₁₋₄ alkyl;

each R⁶ is

- halo,
- CN,
- NO₂,
- CH₃,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C₁₋₄ alkyl, or C₁₋₄ alkoxy, or
- NR^{9g}R^{9h};

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, or R^{7e} is

- H, or
- C₁₋₄ alkyl optionally substituted with one OH, C₁₋₄ alkoxy;

each R^{8a}, or R^{8b} is independently selected from

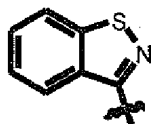
- H, and
- C₁₋₄ alkyl optionally substituted with one or more independently selected OH, C₁₋₄ alkoxy, or phenyl;

each R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, and R^{9h} is independently selected from H, and C₁₋₄ alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof;

provided that:

- R¹ and R² are not simultaneously H, and



- when R¹ is Me, then Cy is not

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

[0023] In a particular example, the compounds of the disclosure may exhibit selectivity towards the ADAMTS protease family, in particular towards the ADAMTS-5. In a further particular example, the compounds of the disclosure may show low activity on MMP family members, in particular MMP8 and/or MMP12. Such selectivity may result in improved drug safety and/or reduce off-target associated risks. In another more particular example, the compounds of the disclosure surprisingly exhibit activity against ADAMTS-5 compared to structurally related close analogues.

[0024] In a further example, 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 conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In another aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as described herein.

[0025] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used. In yet another aspect, the present invention provides a compound or pharmaceutically acceptable salt thereof as described herein or a pharmaceutical composition as describe herein for use in medicine.

[0026] 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 conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0027] 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 conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In yet another aspect, the present invention provides a compound or pharmaceutically acceptable salt thereof as described herein or a pharmaceutical composition as described herein for use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0028] In a particular example, the compounds of the disclosure are provided for use in the prophylaxis and/or treatment of osteoarthritis.

[0029] In additional examples, this disclosure provides methods for synthesizing the compounds of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0030] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0031] It will be appreciated that compounds of the disclosure may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0032] 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.

[0033] 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.