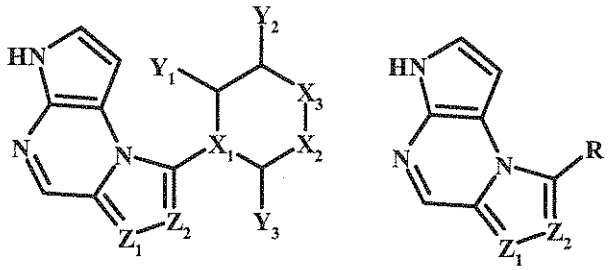
JAK1, wherein preferred compounds are selective for JAK3 of the JAK kinases, and are useful novel compounds for the treatment of auto-immune and inflammatory diseases.

The present application provides compounds of Formulae **I-II**,



I **II**

wherein the variables R, X^1, X^2, X^3, Y^1, Y^2, Y^3, Z^1, and Z^2 are defined as described herein, which inhibit JAK and are useful for the treatment of auto-immune and inflammatory diseases.

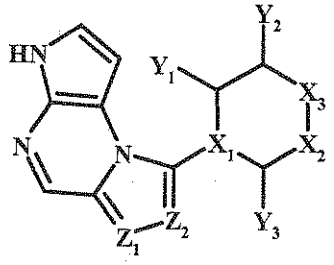
In one ~~aspect~~embodiment, the application provides a method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I**.

In one ~~aspect~~embodiment, the application provides a method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **II**.

The application provides a pharmaceutical composition comprising the compound of Formula **I**, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

The application provides a pharmaceutical composition comprising the compound of Formula **II**, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

The application provides a compound of Formula **I**



I

wherein:

Z^1 is CH or N;

Z^2 is CH or N;

X^1 is CH or N;

X^2 is CH_2, $NS(=O)_2R^1$, or $NC(=O)R^{1'}$;

R^1 is lower alkyl;

$R^{1'}$ is H, amino, or $R^{1''}$;

$R^{1''}$ is lower alkyl, optionally substituted with one or more $R^{1'''}$;

$R^{1'''}$ is halogen, lower alkoxy, cyano, or amino;

X^3 is CHR^2 or $S(=O)_2$;

R^2 is H or lower alkyl;

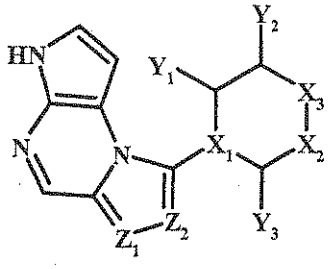
Y^1 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

Y^2 is H or lower alkyl; and

Y^3 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

or a pharmaceutically acceptable salt thereof.

In a first aspect, there is provided a compound of Formula I



I

wherein:

Z^1 is CH;

Z^2 is CH or N;

X^1 is CH or N;

X^2 is CH_2, $NS(=O)_2R^1$, or $NC(=O)R^{1'}$;

R^1 is lower alkyl;

$R^{1'}$ is H, amino, or $R^{1''}$;

$R^{1''}$ is lower alkyl, optionally substituted with one or more $R^{1'''}$;

$R^{1'''}$ is halogen, lower alkoxy, cyano, or amino;

X^3 is CHR^2 or $S(=O)_2$;

R^2 is H or lower alkyl;

Y^1 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

Y^2 is H or lower alkyl; and

Y^3 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

or a pharmaceutically acceptable salt thereof.

In one variation of Formula **I**, Z^1 is CH and Z^2 is CH.

In one variation of Formula **I**, X^1 is CH.

In one variation of Formula **I**, X^1 is CH, Z^1 is CH, and Z^2 is CH.

In one variation of Formula **I**, X^1 is N.

In one variation of Formula **I**, X^1 is N, Z^1 is CH, and Z^2 is CH.

In one variation of Formula **I**, X^3 is $S(=O)_2$.

Z^1 is CH or N;

Z^2 is CH or N;

R is lower alkyl, lower alkoxy, amino, cycloalkyl or heterocycloalkyl, optionally substituted with one more R^1; and

R^1 is lower alkyl, halogen, lower haloalkyl, lower alkoxy, lower alkylsulfonyl, or $C(=O)R^2$;

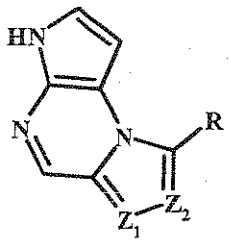
R^2 is H, amino, or R^3;

R^3 is lower alkyl, optionally substituted with one or more R^4; and

R^4 is halogen, lower alkoxy, cyano, or amino;

or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided a compound of Formula **II**



II

wherein:

Z^1 is CH;

Z^2 is CH or N;

R is cycloalkyl or heterocycloalkyl, optionally substituted with one or more R^1; and

R^1 is lower alkyl, halogen, lower haloalkyl, lower alkoxy, lower alkylsulfonyl, or $C(=O)R^2$;

R^2 is H, amino, or R^3;

R^3 is lower alkyl, optionally substituted with one or more R^4; and

R^4 is halogen, lower alkoxy, cyano, or amino;

or a pharmaceutically acceptable salt thereof.

In one variation of Formula **II**, R is lower alkyl.

In one variation of Formula **II**, R is lower alkoxy.

In one variation of Formula **II**, R is amino.

In one variation of Formula **II**, R is cycloalkyl.

In one variation of Formula **II**, R is heterocycloalkyl.

In one variation of Formula **II**, R is heterocycloalkyl, R^1 is $C(=O)R^2$, R^2 is R^3, R^3 is lower alkyl, and R^4 is cyano.

In one ~~aspect~~embodiment, the application provides a method for treating asthma comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for treating arthritis comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for treating rheumatoid arthritis comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one variation of the above method, the above method further comprises administering an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

In one ~~aspect~~embodiment, the application provides a method for treating an inflammatory condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for inhibiting T-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for inhibiting T-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one variation of the above method, the proliferative disorder is cancer.

In one ~~aspect~~embodiment, the application provides a method for treating a B-cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for treating an immune disorder including lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes, complications from organ transplants, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and Leukemia, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for preventing or treating all forms of organ rejection, including acute allograft or xenograft rejection and chronic allograft or xenograft rejection, of vascularized or non-vascularized transplants, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for inhibiting JAK3 activity comprising administering the compound of Formula **I** or Formula **II**, wherein the compound exhibits an IC_{50} of 50 micromolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one variation of the above method, the compound exhibits an IC_{50} of 100 nanomolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one variation of the above method, the compound exhibits an IC_{50} of 10 nanomolar or less in an *in vitro* biochemical assay of JAK3 activity.

In one ~~aspect~~embodiment, the application provides a method for treating an inflammatory condition comprising co-administering to a patient in need thereof an anti-inflammatory compound in combination with a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

In one ~~aspect~~embodiment, the application provides a method for treating an immune disorder comprising co-administering to a patient in need thereof an immunosuppressant compound in combination with a therapeutically effective amount of the compound of Formula **I** or Formula **II**.

The application provides a pharmaceutical composition comprising the compound of Formula **I** or Formula **II**, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a third aspect, there is provided a pharmaceutical composition comprising the compound according to the second aspect, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

In one variation, the above pharmaceutical composition further comprises an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

In one ~~aspect~~embodiment, the application provides a use of the compound of Formula **I** or Formula **II** in the manufacture of a medicament for the treatment of an inflammatory disorder.

In one ~~aspect~~embodiment, the application provides a use of the compound of Formula **I** or Formula **II** in the manufacture of a medicament for the treatment of an autoimmune disorder.

In a further ~~aspect~~embodiment, the application provides the compound Formula **I** or Formula **II** for use in the treatment of an inflammatory disorder.

In a further ~~aspect~~embodiment, the application provides the compound Formula **I** or Formula **II** for use in the treatment of an autoimmune disorder.

Definitions

The phrase “a” or “an” entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

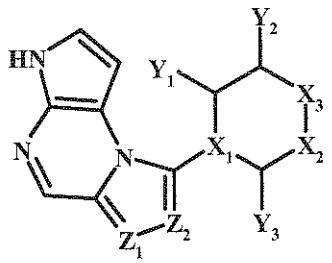
The phrase "as defined herein above" refers to the broadest definition for each group as provided in the Summary of the Invention or the broadest claim. In all other embodiments provided below, substituents which can be present in each embodiment and which are not explicitly defined retain the broadest definition provided in the Summary of the Invention.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

Claims

1. A compound of Formula I



I

wherein:

Z^1 is CH ~~or N~~;

Z^2 is CH or N;

X^1 is CH or N;

X^2 is CH_2, $NS(=O)_2R^1$, or $NC(=O)R^{1'}$;

R^1 is lower alkyl;

$R^{1'}$ is H, amino, or $R^{1''}$;

$R^{1''}$ is lower alkyl, optionally substituted with one or more $R^{1'''}$;

$R^{1'''}$ is halogen, lower alkoxy, cyano, or amino;

X^3 is CHR^2 or $S(=O)_2$;

R^2 is H or lower alkyl;

Y^1 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

Y^2 is H or lower alkyl; and

Y^3 is H, lower alkyl, lower alkoxy, halogen, or lower haloalkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Z^1 is CH and Z^2 is CH.

3. The compound ~~according to either~~of claim ~~1 or~~ 2, wherein X^1 is CH.

4. The compound ~~according to either~~ of claim ~~1 or~~ 2, wherein X^1 is N.

5. The compound ~~according to any one~~ of claims ~~31 to~~ 4, wherein X^3 is $S(=O)_2$.

6. The compound ~~according to any one~~ of claims ~~1 to 4~~3, wherein X^3 is CH_2.

7. The compound ~~according to any one~~ of claims ~~1 to~~ 6, wherein X^2 is $NS(=O)_2CH_2CH_3$.

8. The compound ~~according to any one~~ of claims ~~1 to~~ 7, wherein Y^2 is H and Y^3 is H.

9. The compound ~~according to any one~~ of claims ~~1 to~~ 8, wherein Y^1 is methyl.

10. The compound of claim 1, wherein Z^1 is ~~N~~ CH and Z^2 is N.

11. The compound ~~according to either~~of claim ~~1 or~~ 10, wherein Y^2 is H and X^3 is CH_2.

12. The compound ~~according to any one~~ of claims ~~1, 10 or~~ 11 , wherein X^2 is $NS(=O)_2CH_2CH_3$.

13. The compound ~~according to any one~~ of claims ~~1, 10 to~~ 12, wherein Y^1 is methyl.

14. The compound ~~according to any one~~ of claims ~~1, 10 or~~ 11-, wherein Y^1 is H and X^2 is CH_2.

15. The compound ~~according to any one~~ of claims ~~1, 10, 11 or~~ 14, wherein Y^3 is methyl.

16. The compound of claim 1 selected from the group consisting of:

8-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-3*H*-3,4,8a-triaza-*as*-indacene;

8-Cyclohexyl-3*H*-3,4,8a-triaza-*as*-indacene;

8-(2-Methyl-piperidin-1-yl)-3*H*-3,4,8a-triaza-*as*-indacene;

8-((3S,4S)-1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-3*H*-3,4,8a-triaza-*as*-indacene;

8-((3S,4R)-1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-3*H*-3,4,8a-triaza-*as*-indacene;

1-((1R,2S)-2-Methyl-cyclohexyl)-6*H*-2,3,5,6,8b-pentaaza-*as*-indacene;

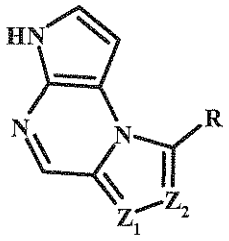
1-((3R,4R)-1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-6*H*-2,3,5,6,8b-pentaaza-*as*-indacene;

1-Cyclohexyl-6H-2,3,5,6,8b-pentaaza-as-indacene;

3-[(3S,4S)-4-Methyl-3-(6*H*-2,3,5,6,8b-pentaaza-*as*-indacen-1-yl)-piperidin-1-yl]-3-oxo-propionitrile;

1-Cyclohexyl-6*H*-2,5,6,8b-tetraaza-*as*-indacene;

17. A compound of Formula **II**



II

wherein:

Z^1 is CH ~~or N~~;

Z^2 is CH or N;

R is ~~lower alkyl, lower alkoxy, amino,~~ cycloalkyl or heterocycloalkyl, optionally substituted with one or more R^1; and

R^1 is lower alkyl, halogen, lower haloalkyl, lower alkoxy, lower alkylsulfonyl, or $C(=O)R^2$;

R^2 is H, amino, or R^3;

R^3 is lower alkyl, optionally substituted with one or more R^4; and

R^4 is halogen, lower alkoxy, cyano, or amino;

or a pharmaceutically acceptable salt thereof.

~~18. A method for treating an inflammatory or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 17.~~

~~19. The method of claim 18, further comprising administering an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.~~

~~20. A method for treating an inflammatory condition comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 17.~~

~~21. A method for treating asthma comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 17.~~

~~22. A method for treating rheumatoid arthritis comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to17.~~

~~23~~18. A pharmaceutical composition comprising the compound of ~~any one of~~ claims ~~1 to~~ 17, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

~~24~~19. The pharmaceutical composition of claim ~~23~~18, further comprising an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

~~25. The compound of any one of claims 1 to 17 for use in the treatment of an inflammatory disorder.~~

~~26 The compound of any one of claims 1 to 17 for use in the treatment of an autoimmune disorder.~~

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