

R² is hydrogen or alkyl;

R³ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthioalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein aryl or heteroaryl by itself
5 as part of aralkyl or heteroaralkyl is optionally substituted with R^d, R^e, and/or R^f independently selected from alkyl, alkoxy, hydroxy, halo, haloalkyl, haloalkoxy, cyano, nitro, carboxy, alkoxycarbonyl, amino, alkylamino, and dialkylamino;

R⁴ is hydrogen or alkyl; and

R⁵ is -C(O)R⁶ where R⁶ is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein aryl or heteroaryl by itself or
10 as part of aralkyl or heteroaralkyl is optionally substituted with R^g, R^h, and/or Rⁱ independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, optionally substituted
15 heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy, cyano, nitro, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, and sulfonylamino; or

R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 5 to 7 membered heterocycloamino ring; or

20 a pharmaceutically acceptable salt thereof.

In a second aspect, this disclosure is directed to a pharmaceutical composition comprising a compound Formula (I) (or any of the embodiments thereof described herein), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

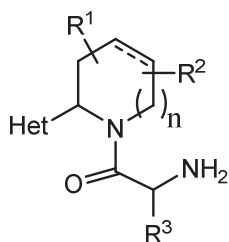
In some examples, this disclosure is directed to a method of treating a disease treatable by
25 inhibiting NF-κB activation comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in a pharmaceutical composition comprising a compound of Formula (I) (or any of the embodiments thereof described herein) and a pharmaceutically acceptable excipient. In one embodiment the diseases are inflammatory diseases including, autoimmune diseases, pain, allergies, asthma,
30 chronic obstructive pulmonary disease and sepsis. In another embodiment the diseases are rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's

disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.

In another aspect, the disclosure is directed to a compound of Formula (I) (or any embodiments thereof described herein) or a pharmaceutically acceptable salt thereof for use as a medicament. In one embodiment, the compound of Formula (I) (and any embodiments thereof described herein) or a pharmaceutically acceptable salt thereof is useful for the treatment of inflammatory diseases including, autoimmune diseases, pain, allergies, asthma, chronic obstructive pulmonary disease and sepsis. In another embodiment the diseases are rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.

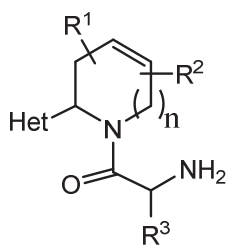
In some examples provided a compound Formula (I) or a pharmaceutically acceptable salt thereof (and any embodiments thereof disclosed herein) for use in treating a disease in a patient in which NF-kB activation contributes to the pathology and/or symptoms of the disease. In one example the diseases are inflammatory diseases including, autoimmune diseases, pain, allergies, asthma, chronic obstructive pulmonary disease and sepsis. In another example the diseases are rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.

In some examples, provided is an intermediate of Formula (II):



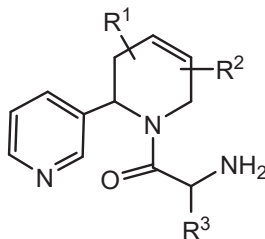
(II)

where dashed line, n, Het, R¹, R², and R³ are as defined for Formula (I) above (including examples thereof disclosed herein). In one aspect, the intermediate has the structure (IIB):



(IIB)

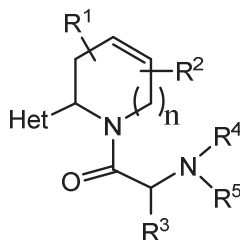
where n, Het, R¹, R², and R³ are as defined for Formula (I) (including examples thereof disclosed herein). In another aspect, the intermediate has the structure (IIB'):



(IIB')

where R¹, R², and R³ are as defined for Formula (I) (including examples thereof disclosed herein) and pyridyl is optionally substituted with R^a, R^b, and/or R^c.

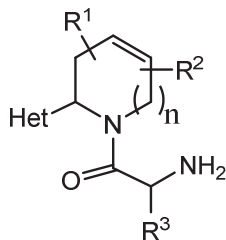
In a seventh aspect, provided is a process of making a compound of Formula (IB):



(IB)

where, n, Het, R¹, R², and R³ are as defined above, R⁴ is hydrogen or alkyl and R⁵ is -COR⁶ where R⁶ is as defined above, comprising:

reacting a compound of formula (IIB):



(IIB)

where dashed line, n, Het, R¹, R², and R³ are as defined above;

(i) with a compound of formula R^6COLG where R^6 is as defined in Formula (I) above and LG is a leaving group under acylating reaction conditions; or

(ii) with a compound of formula R^6COOH under amino acid coupling reaction conditions;

5 (iii) optionally converting the compound of Formula (IB) obtained from step (i) or (ii) to an acid addition salt; or

(iv) optionally converting the compound of Formula (IB) obtained from step (i) or (ii) to the free base.

In another aspect, provided is a use of the pharmaceutical composition as described herein
10 in the manufacture of a medicament for treating a disease treatable by inhibiting NF- κ B activation.

Detailed Description

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

15 “Alkyl” means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like.

“Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms unless
20 otherwise stated e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

“Alkylthio” means a -SR radical where R is alkyl as defined above, e.g., methylthio, ethylthio, and the like.

“Alkylsulfonyl” means a -SO₂R radical where R is alkyl as defined above, e.g.,
25 methylsulfonyl, ethylsulfonyl, and the like.

“Amino” means a -NH₂.

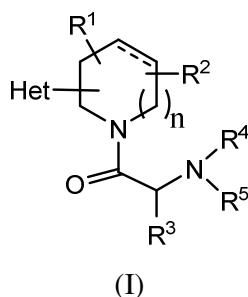
“Alkylamino” means a -NHR radical where R is alkyl as defined above, e.g., methylamino, ethylamino, propylamino, or 2-propylamino, and the like.

- “Aminoalkyl” means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with -NR'R”
- 5 where R' and R” are independently hydrogen or alkyl as defined above, e.g., aminomethyl, aminoethyl, methylaminomethyl, and the like.

“Alkoxy” means an -OR radical where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

What is Claimed:

1. A compound of Formula (I):



5

wherein:

n is 0, 1, or 2;

dashed line is an optional bond;

Het is heteroaryl optionally substituted with R^a, R^b, and/or R^c independently selected from
10 alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, amino, alkylamino, dialkylamino,
carboxy, and alkoxycarbonyl;

R¹ is hydrogen or alkyl;

R² is hydrogen or alkyl;

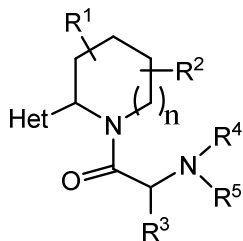
R³ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl,
15 alkylthioalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl,
aminocarbonylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, wherein aryl or heteroaryl by itself
as part of aralkyl or heteroaralkyl is optionally substituted with R^d, R^e, and/or R^f independently
selected from alkyl, alkoxy, hydroxy, halo, haloalkyl, haloalkoxy, cyano, nitro, carboxy,
alkoxycarbonyl, amino, alkylamino, and dialkylamino;

20 R⁴ is hydrogen or alkyl; and

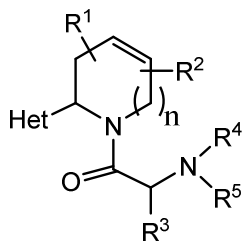
R⁵ is -C(O)R⁶ where R⁶ is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl,
cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein aryl or heteroaryl by itself or
as part of aralkyl or heteroaralkyl is optionally substituted with R^g, R^h, and/or Rⁱ independently
selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy,
25 cycloalkylalkyloxy, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally
substituted heteroaryloxy, optionally substituted heteroaralkyloxy, optionally substituted
heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy,
cyano, nitro, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, and
sulfonylamino; or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 5 to 7 membered heterocycloamino ring; or
a pharmaceutically acceptable salt thereof.

- 5 2. The compound of claim 1 wherein the compound has structure (IA):



3. The compound of claim 1 wherein the compound has structure (IB):



10

4. The compound of any one of claims 1-3 wherein n is 1, 2, or 3.

5. The compound of any one of claims 1-4 wherein n is 1.

- 15 6. The compound of any one of claims 1-3 wherein n is 0 or 2.

7. The compound of any one of claims 1-3 wherein n is 0.

8. The compound of any one of claims 1-3 wherein n is 2.

20

9. The compound of any one of claims 1-8 wherein R^4 is hydrogen or alkyl and R^5 is $-C(O)R^6$ where R^6 is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or heterocycloalkyl wherein aryl or heteroaryl by itself or as part of aralkyl or heteroaralkyl are optionally substituted with R^g , R^h , and/or R^i independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, optionally substituted aralkyloxy, optionally
- 25

substituted heteroaryloxy, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy, cyano, nitro, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, and sulfonylamino.

- 5 10. The compound of claim 9 wherein R⁵ is aryl or heteroaryl optionally substituted with R^g, R^h, and/or Rⁱ.
11. The compound of claim 9 wherein R⁵ is aralkyl or heteroaralkyl optionally substituted with R^g, R^h, and/or Rⁱ.
- 10 12. The compound of claim 9 wherein R⁵ is phenyl optionally substituted with R^g, R^h, and/or Rⁱ.
13. The compound of any one of claims 1 to 12 wherein R^g is alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, or cyano and R^h and Rⁱ are independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, or
- 15 13. The compound of any one of claims 1 to 12 wherein R^g is alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, or cyano and R^h and Rⁱ are independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, or
- 20 14. The compound of any one of claims 1 to 12 wherein R^g, R^h and Rⁱ are independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, amino, acylamino, preferably, methyl, ethyl, methoxy, ethoxy, chloro, fluoro, trifluoromethyl, trifluoromethoxy, hydroxy, acetylamino, butanoylamino, and pentanoylamino.
- 25 15. The compound of any one of claims 1 to 8 wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 5 to 7 membered heterocycloamino ring.
- 30 16. The compound of any one of claims 1 to 15 wherein R¹ and R² are independently hydrogen or methyl, preferably hydrogen.
17. The compound of any one of claims 1 to 16 wherein when both R¹ and R² are alkyl, they are not bound to the same ring carbon.

18. The compound of any one of claims 1 to 17 wherein Het is pyridinyl, pyrimidinyl, pyrazinyl, furanyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, or indolyl, each ring optionally substituted with R^a, R^b, and R^c independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, amino, alkylamino, dialkylamino, carboxy, and alkoxycarbonyl.

19. The compound of any one of claims 1 to 17 wherein R^a, R^b, and R^c independently selected from methyl, ethyl, methoxy, ethoxy, chloro, fluoro, trifluoromethyl, trifluoromethoxy, cyano, amino, methylamino, or dimethylamino.

20. The compound of any one of claims 1 to 17 wherein Het is pyridin-2-yl.

21. The compound of any one of claims 1 to 20 wherein R³ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthioalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl wherein aryl or heteroaryl by itself or in aralkyl and heteroaralkyl is optionally substituted with R^d, R^e, and/or R^f independently selected from alkyl, alkoxy, hydroxy, halo, haloalkyl, haloalkoxy, cyano, nitro, carboxy, alkoxycarbonyl, amino, alkylamino, and dialkylamino.

22. The compound of any one of claims 1 to 20 wherein R³ is hydrogen or alkyl, preferably methyl, ethyl, propyl, isopropyl, sec-propyl, n-, sec, iso, tert-butyl.

23. The compound of any one of claims 1 to 20 wherein R³ is aralkyl optionally substituted with R^d, R^e, and/or R^f, preferably R³ is benzyl or phenethyl, more preferably benzyl optionally substituted with R^d, R^e, and/or R^f, even more preferably R³ is benzyl.

24. The compound of any one of claims 1 to 20 wherein R³ is cycloalkylalkyl optionally substituted with R^d, R^e, and/or R^f, preferably R³ is cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, or cyclohexylmethyl optionally substituted with R^d, R^e, and/or R^f.

25. The compound of any one of claims 1 to 20 wherein R³ is heteroaralkyl (e.g., thienylmethyl, furanylmethyl, pyridinylmethyl, quinolinylmethyl, isoquinolinylmethyl, indolylmethyl, or indazolylmethyl) optionally substituted with R^d, R^e, and/or R^f.

26. The compound of any one of claims 1 to 20 wherein R^3 is hydroxyalkyl, alkoxyalkyl, aminoalkyl, preferably R^3 is hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, aminomethyl, or aminobutyl.
- 5 27. The compound of any one of claims 1 to 26 wherein the stereochemistry at carbon to which R^3 is attached is (S).
28. The compound of any one of claims 1 to 26 wherein the stereochemistry at carbon to which R^3 is attached is (R).
- 10 29. A pharmaceutical composition comprising a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
- 15 30. Use of the pharmaceutical composition of claim 29 in the manufacture of a medicament for treating a disease treatable by inhibiting NF- κ B activation.
31. The use of claim 30 wherein the disease is an inflammatory disease.
- 20 32. The use of claim 31 wherein the disease is selected from the group consisting of autoimmune disease, pain, allergies, asthma, chronic obstructive pulmonary disease and sepsis.
- 25 33. The use of claim 30 wherein the disease is selected from the group consisting of rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.
- 30 34. The pharmaceutical composition of claim 29 for use as a medicament.