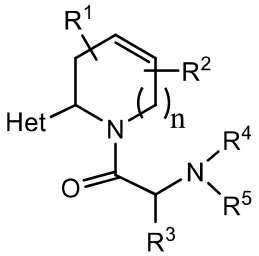
(i) with a compound of formula R^6COLG where R^6 is as defined in Formula (I) above and LG is a leaving group under acylating reaction conditions; or

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

(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 herein is a compound of Formula (IB):



(IB)

wherein:

n is 0, 1, or 2;

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

R^1 is hydrogen or alkyl;

R^2 is hydrogen or alkyl;

R^3 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 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;

R^4 is hydrogen or alkyl; and

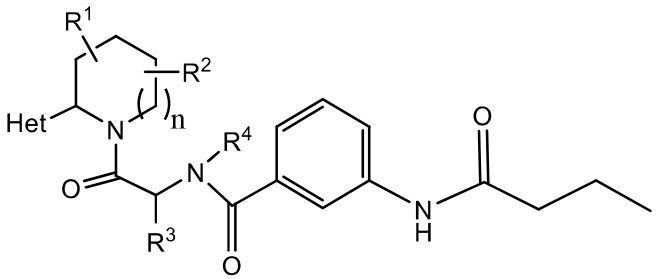
R^5 is $-C(O)R^6$ where R^6 is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein aryl or heteroaryl by itself or as part of aralkyl or heteroaralkyl is optionally substituted with R^g, R^h, and/or R^i independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, 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.

In another aspect, provided herein is a compound having the structure:



wherein:

n is 0, 1, or 2;

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

R^1 is hydrogen or alkyl;

R^2 is hydrogen or alkyl;

R^3 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 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;

R^4 is hydrogen or alkyl; or

a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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

In yet another aspect, provided herein is the pharmaceutical composition as described herein for use as a medicament.

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:

"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 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 $–SO_2R$ radical where R is alkyl as defined above, e.g., methylsulfonyl, ethylsulfonyl, and the like.

"Amino" means a $–NH_2$.

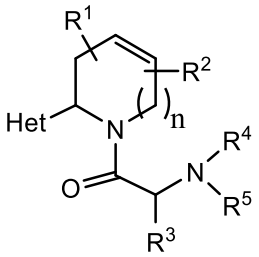
"Alkylamino" means a -NHR radical where R is alkyl as defined above, e.g., methylamino, ethylamino, propylamino, or 2-propylamino, and the like.

"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" 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 (IB):



(IB)

wherein:

n is 0, 1, or 2;

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

R^1 is hydrogen or alkyl;

R^2 is hydrogen or alkyl;

R^3 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 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;

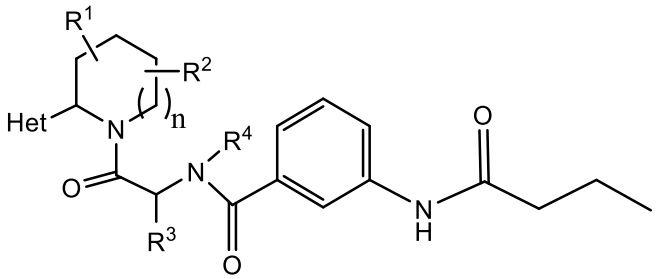
R^4 is hydrogen or alkyl; and

R^5 is -C(O)R^6 where R^6 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 R^i independently selected from alkyl, alkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyloxy, 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.

2. A compound having the structure:



wherein:

n is 0, 1, or 2;

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

R^1 is hydrogen or alkyl;

R^2 is hydrogen or alkyl;

R^3 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 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;

R^4 is hydrogen or alkyl; or

a pharmaceutically acceptable salt thereof.

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

4. The compound of any one of claims 1-3 wherein n is1.

5. The compound of any one of claims 1-2 wherein n is 0 or 2.

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

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

8. The compound of any one of claims 1-7 wherein R^4 is hydrogen or alkyl and R^5, where present, 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 substituted heteroaryloxy, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylalkyloxy, halo, haloalkyl, haloalkoxy, cyano, nitro, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, acylamino, and sulfonylamino.

9. The compound of claim 8 wherein R^5 is aryl or heteroaryl optionally substituted with R^g, R^h, and/or R^i.

10. The compound of claim 8 wherein R^5 is aralkyl or heteroaralkyl optionally substituted with R^g, R^h, and/or R^i.

11. The compound of claim 8 wherein R^5 is phenyl optionally substituted with R^g, R^h, and/or R^i.

12. The compound of any one of claims 1 to 11 wherein R^g is alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, or cyano and R^h and R^i 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 sulfonylamino.

13. The compound of any one of claims 1 to 11 wherein R^g, R^h and R^i 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.

14. The compound of any one of claims 1 and 3 to 7 wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 5 to 7 membered heterocycloamino ring.

15. The compound of any one of claims 1 to 14 wherein R^1 and R^2 are independently hydrogen or methyl, preferably hydrogen.

16. The compound of any one of claims 1 to 15 wherein when both R^1 and R^2 are alkyl, they are not bound to the same ring carbon.

17. The compound of any one of claims 1 to 16 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.

18. The compound of any one of claims 1 to 16 wherein R^a, R^b, and R^c independently selected from methyl, ethyl, methoxy, ethoxy, chloro, fluoro, trifluoromethyl, trifluoromethoxy, cyano, amino, methylamino, or dimethylamino.

19. The compound of any one of claims 1 to 16 wherein Het is pyridin-3-yl.

20. The compound of any one of claims 1 to 19 wherein R^3 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.

21. The compound of any one of claims 1 to 19 wherein R^3 is hydrogen or alkyl, preferably methyl, ethyl, propyl, isopropyl, sec-propyl, n-, sec, iso, tert-butyl.

22. The compound of any one of claims 1 to 19 wherein R^3 is aralkyl optionally substituted with R^d, R^e, and/or R^f , preferably R^3 is benzyl or phenethyl, more preferably benzyl optionally substituted with R^d, R^e, and/or R^f, even more preferably R^3 is benzyl.

23. The compound of any one of claims 1 to 19 wherein R^3 is cycloalkylalkyl optionally substituted with R^d, R^e, and/or R^f, preferably R^3 is cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, or cyclohexylmethyl optionally substituted with R^d, R^e, and/or R^f.

24. The compound of any one of claims 1 to 19 wherein R^3 is heteroaralkyl (e.g., thienylmethyl, furanylmethyl, pyridinylmethyl, quinolinylmethyl, isoquinolinylmethyl, indolylmethyl, or indazolylmethyl) optionally substituted with R^d, R^e, and/or R^f.

25. The compound of any one of claims 1 to 19 wherein R^3 is hydroxyalkyl, alkoxyalkyl, aminoalkyl, preferably R^3 is hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, aminomethyl, or aminobutyl.

26. The compound of any one of claims 1 to 25 wherein the stereochemistry at carbon to which R^3 is attached is (S).

27. The compound of any one of claims 1 to 25 wherein the stereochemistry at carbon to which R^3 is attached is (R).

28. A pharmaceutical composition comprising a compound of any one of claims 1-27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

29. Use of the pharmaceutical composition of claim 28 in the manufacture of a medicament for treating a disease treatable by inhibiting NF-kB activation.

30. The use of claim 29 wherein the disease is an inflammatory disease.

31. The use of claim 30 wherein the disease is selected from the group consisting of autoimmune disease, pain, allergies, asthma, chronic obstructive pulmonary disease and sepsis.

32. The use of claim 29 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, periodonitis, inflammatory lung disease, and lupus nephritis.

33. The pharmaceutical composition of claim 28 for use as a medicament.