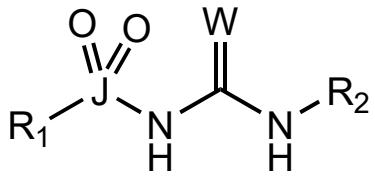
CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

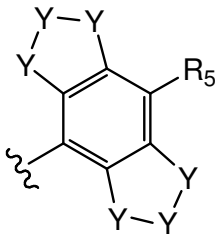
wherein

W is selected from O, S and Se;

J is selected from S and Se;

R_1 is selected from the group consisting of 5-membered and 6-membered heterocyclyl, all of which are optionally substituted, wherein any optional substituent is independently selected from the group consisting of C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, hydroxyalkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6-C_{12} aryl, aryloxy, heteroaryl, heterocyclyl, halo, hydroxyl, halogenated alkyl, amino, alkylamino, arylamino, acyl, amido, CN, NO_2, N_3, CH_2OH, $CONH_2$, $CONR_{24}R_{25}$, CO_2R_{24}, CH_2OR_{24}, $NHCOR_{24}$, $NHCO_2R_{24}$, C_1-C_3 alkylthio, sulfate, sulfonic acid, sulfonate esters, phosphonic acid, phosphate, phosphonate, mono-, di-, or triphosphate esters, trityl, monomethoxytrityl, $R_{24}SO$, $R_{24}SO_2$, CF_3S, CF_3SO_2, and trialkylsilyl, wherein R_{24} and R_{25} are each independently selected from H and C_1-C_{10} alkyl;

R_2 is selected from a 2,6-dialkylphenyl, a 2,6-dialkyl-4-halophenyl, a 2,6-dicycloalkylphenyl, a 2,6-dicycloalkyl-4-halophenyl, and:



wherein each incidence of Y is independently selected from C, N, S and O, which are optionally substituted, wherein any optional substituent is independently selected from the group consisting of C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, hydroxyalkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6-C_{12} aryl, aryloxy, heteroaryl, heterocyclyl, halo, hydroxyl, halogenated alkyl, amino, alkylamino, arylamino, acyl, amido, CN, NO_2, N_3, CH_2OH, $CONH_2$, $CONR_{24}R_{25}$, CO_2R_{24}, CH_2OR_{24}, $NHCOR_{24}$, $NHCO_2R_{24}$, C_1-C_3 alkylthio, sulfate, sulfonic acid, sulfonate esters, phosphonic acid, phosphate, phosphonate, mono-, di-, or triphosphate esters, trityl, monomethoxytrityl, $R_{24}SO$, $R_{24}SO_2$, CF_3S, CF_3SO_2, and trialkylsilyl, wherein R_{24} and R_{25} are each independently selected from H and C_1-C_{10} alkyl;

R_5 is selected from the group consisting of hydrogen, halo, cyano, amide, sulphonamide, acyl, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_5 cycloalkyl and C_1-C_6 alkoxy, all of which groups are optionally substituted with halo, cyano or C_1-C_6 alkoxy; and

both R_1 is directly bonded to J and R_2 is directly bonded to the adjacent nitrogen, via a carbon atom.

2. The compound of claim 1, wherein R_1 is a 6-membered heterocyclyl, all of which are optionally substituted as defined in claim 1.

3. The compound of any one of the preceding claims, wherein R_1 is a fully saturated heterocyclyl, all of which are optionally substituted as defined in claim 1.

4. The compound of any one of the preceding claims, wherein R_1 is a nitrogen heterocyclyl, all of which are optionally substituted as defined in claim 1.

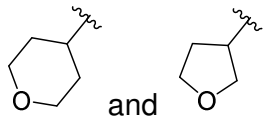
5. The compound of any one of the preceding claims, wherein R_1 is selected from the group consisting of tetrahydrofuran, tetrahydropyran, pyran, pyrrolidine, morpholine, piperazine and piperidine, all of which are optionally substituted as defined in claim 1.

6. The compound of any one of the preceding claims, wherein R_1 is selected from the group consisting of tetrahydrofuran, tetrahydropyran, pyrrolidine, morpholine, piperazine and piperidine, all of which are optionally substituted as defined in claim 1.

7. The compound of any one of the preceding claims, wherein R_1 is selected from the group consisting of pyrrolidine, piperazine and piperidine, all of which are optionally substituted as defined in claim 1.

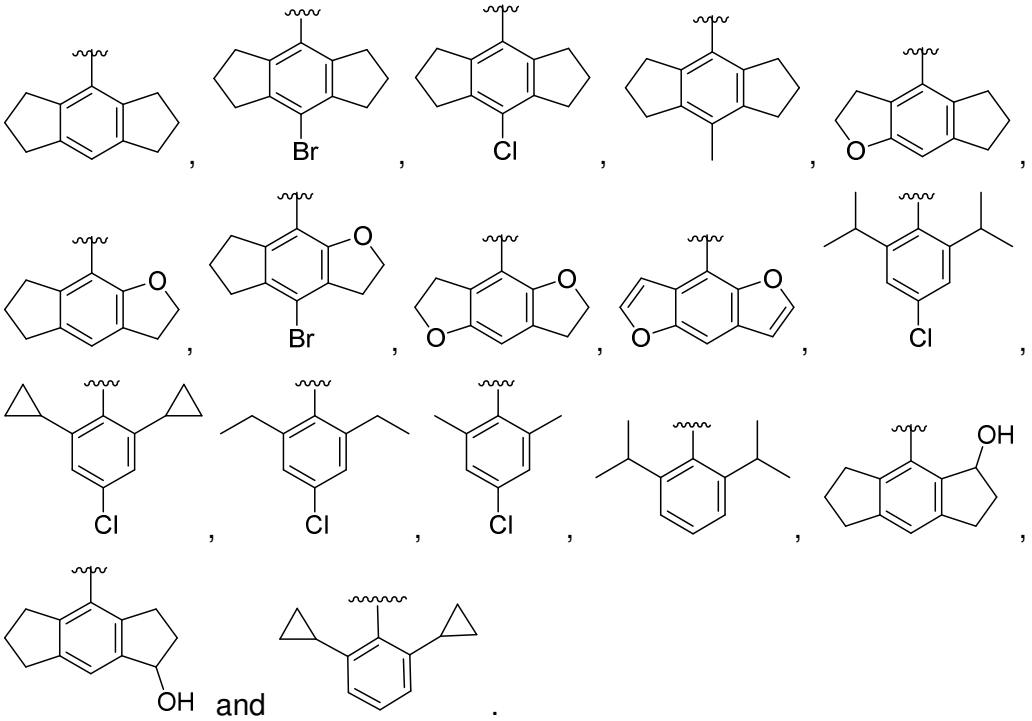
8. The compound of any one of the preceding claims, wherein R_1 is piperidine optionally substituted as defined in claim 1.

9. The compound of any one of claims 1, 2, 3, 5 or 6, wherein R_1 is selected from the group consisting of:



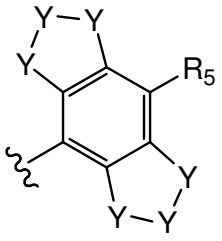
;

and in combination with each such R_1 group, R_2 is independently selected from the group consisting of:



and .

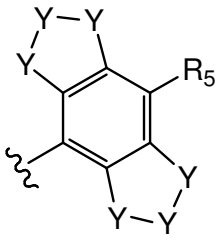
10. The compound of any one of the preceding claims, wherein R_2 is selected from:



,

wherein Y and R_5 are as defined in any one of the preceding claims.

11. The compound of any one of the preceding claims, wherein R_2 is selected from:



,

wherein each incidence of Y is a carbon and R_5 is hydrogen or halo.

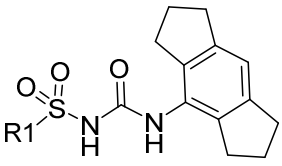
12. The compound of any one of the preceding claims, wherein R_2 is selected from a substituted or hydrogenated indacene, a 2,6-dialkylphenyl, a 2,6-dialkyl-4-halophenyl, a 2,6-dicycloalkylphenyl, and a 2,6-dicycloalkyl-4-halophenyl.

13. The compound of any one of the preceding claims, wherein R_2 is selected from hexahydroindacene, 2,6-diisopropylphenyl, 2,6-diisopropyl-4-chlorophenyl, 2,6-dicyclopropylphenyl and 2,6-dicyclopropyl-4-chlorophenyl.

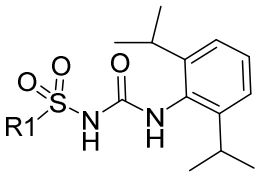
14. The compound of any one of the preceding claims, wherein J is a sulphur atom.

15. The compound of any one of the preceding claims, wherein W is an oxygen atom.

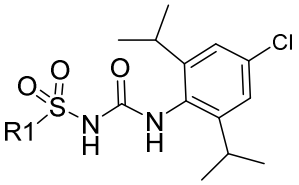
16. The compound of any one of the preceding claims, wherein the compound is a compound of formula (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt or solvate thereof:



formula (Ia)



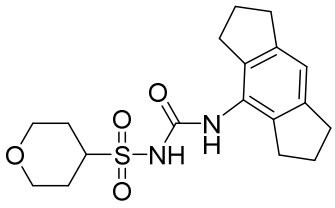
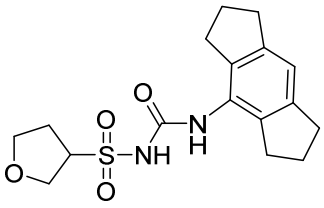
formula (Ib)



formula (Ic)

wherein R_1 is as defined in any one of the preceding claims.

17. The compound of any one of claims 1-3, 5-6 or 9-16, wherein the compound is selected from the group consisting of:


and

,

and pharmaceutically acceptable salts and solvates thereof.

18. The compound or the pharmaceutically acceptable salt or solvate of any one of the preceding claims, wherein the compound, or the pharmaceutically acceptable salt or solvate, is an inhibitor of the NLRP3 inflammasome.

19. A pharmaceutical composition comprising a compound of any one of claim 1 to claim 18, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, diluent and/or excipient.

20. The compound or the pharmaceutically acceptable salt or solvate of any one of claim 1 to claim 18, for use in medicine.

21. The compound or the pharmaceutically acceptable salt or solvate of any one of claim 1 to claim 18, for use in treating or preventing:

(a) a disease, disorder or condition responsive to inhibition of activation of the NLRP3 inflammasome; and/or

(b) a disease, disorder or condition responsive to modulation of one or more of IL-1β, IL-17, IL-18, IL-1α, IL-37, IL-33 and Th17 cells; and/or

(c) a disease, disorder or condition of the immune system; and/or

(d) an inflammatory disease, disorder or condition or an autoimmune disease, disorder or condition; and/or

(e) a disease, disorder or condition of the skin; and/or

(f) a disease, disorder or condition of the cardiovascular system; and/or

(g) a cancer, tumour or other malignancy; and/or

(h) a disease, disorder or condition of the renal system; and/or

(i) a disease, disorder or condition of the gastro-intestinal tract; and/or

(j) a disease, disorder or condition of the respiratory system; and/or

(k) a disease, disorder or condition of the endocrine system; and/or

(l) a disease, disorder or condition of the central nervous system (CNS); and/or

(m) a disease, disorder or condition selected from the group consisting of constitutive inflammation including the cryopyrin-associated periodic syndromes (CAPS): Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease (NOMID); including autoinflammatory diseases: familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammation, antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD); Sweet’s syndrome, chronic nonbacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO); autoimmune diseases including multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren’s syndrome and Schnitzler syndrome; respiratory diseases including chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis and cystic fibrosis; central nervous system diseases including Parkinson’s disease, Alzheimer’s disease, motor neuron disease, Huntington’s disease, cerebral malaria and

brain injury from pneumococcal meningitis; metabolic diseases including Type 2 diabetes, atherosclerosis, obesity, gout, pseudo-gout; ocular diseases including those of the ocular epithelium, age-related macular degeneration (AMD), corneal infection, uveitis and dry eye; kidney disease including chronic kidney disease, oxalate nephropathy and diabetic nephropathy; liver disease including non-alcoholic steatohepatitis and alcoholic liver disease; inflammatory reactions in skin including contact hypersensitivity and sunburn; inflammatory reactions in the joints including osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis; viral infections including alpha virus including Chikungunya and Ross River, and flavivirus including Dengue and Zika viruses, flu, HIV; hidradenitis suppurativa (HS) and other cyst-causing skin diseases; cancers including lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia; polymyositis; stroke; myocardial infarction; Graft versus Host Disease; hypertension; colitis; helminth infection; bacterial infection; abdominal aortic aneurism; wound healing; depression, psychological stress; pericarditis including Dressler's syndrome; ischaemia reperfusion injury; and any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

22. The compound or the pharmaceutically acceptable salt or solvate of any one of claim 1 to claim 18, for use in diagnosing a disease, disorder or condition, wherein the compound or the pharmaceutically acceptable salt or solvate is a labelled compound of any one of claim 1 to claim 18, or a pharmaceutically acceptable salt or solvate thereof, or metal ion chelate complex thereof.

23. Use of the compound or the pharmaceutically acceptable salt or solvate of any one of claim 1 to claim 18, in the manufacture of a medicament for treating or preventing:

(a) a disease, disorder or condition of the immune system; and/or

(b) an inflammatory disease, disorder or condition or an autoimmune disease, disorder or condition; and/or

(c) a disease, disorder or condition of the skin; and/or

(d) a disease, disorder or condition of the cardiovascular system; and/or

(e) a cancer, tumour or other malignancy; and/or

(f) a disease, disorder or condition of the renal system; and/or

(g) a disease, disorder or condition of the gastro-intestinal tract; and/or

(h) a disease, disorder or condition of the respiratory system; and/or

(i) a disease, disorder or condition of the endocrine system; and/or

(j) a disease, disorder or condition of the central nervous system (CNS); and/or

(k) a disease, disorder or condition selected from the group consisting of constitutive inflammation including the cryopyrin-associated periodic syndromes (CAPS): Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease (NOMID); including autoinflammatory diseases: familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammation, antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD); Sweet’s syndrome, chronic nonbacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO); autoimmune diseases

including multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren's syndrome and Schnitzler syndrome; respiratory diseases including chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis and cystic fibrosis; central nervous system diseases including Parkinson's disease, Alzheimer's disease, motor neuron disease, Huntington's disease, cerebral malaria and brain injury from pneumococcal meningitis; metabolic diseases including Type 2 diabetes, atherosclerosis, obesity, gout, pseudo-gout; ocular diseases including those of the ocular epithelium, age-related macular degeneration (AMD), corneal infection, uveitis and dry eye; kidney disease including chronic kidney disease, oxalate nephropathy and diabetic nephropathy; liver disease including non-alcoholic steatohepatitis and alcoholic liver disease; inflammatory reactions in skin including contact hypersensitivity and sunburn; inflammatory reactions in the joints including osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis; viral infections including alpha virus including Chikungunya and Ross River, and flavivirus including Dengue and Zika viruses, flu, HIV; hidradenitis suppurativa (HS) and other cyst-causing skin diseases; cancers including lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia; polymyositis; stroke; myocardial infarction; Graft versus Host Disease; hypertension; colitis; helminth infection; bacterial infection; abdominal aortic aneurism; wound healing; depression, psychological stress; pericarditis including Dressler's syndrome; ischaemia reperfusion injury; and any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

24. Use of the compound or the pharmaceutically acceptable salt or solvate of any one of claim 1 to claim 18, in the manufacture of a medicament for diagnosing a disease, disorder or condition, wherein the medicament comprises a labelled compound of any one of claim 1 to claim 18, or a

pharmaceutically acceptable salt or solvate thereof, or metal ion chelate complex thereof;

wherein the disease, disorder or condition is:

(a) a disease, disorder or condition of the immune system; and/or

(b) an inflammatory disease, disorder or condition or an autoimmune disease, disorder or condition; and/or

(c) a disease, disorder or condition of the skin; and/or

(d) a disease, disorder or condition of the cardiovascular system; and/or

(e) a cancer, tumour or other malignancy; and/or

(f) a disease, disorder or condition of the renal system; and/or

(g) a disease, disorder or condition of the gastro-intestinal tract; and/or

(h) a disease, disorder or condition of the respiratory system; and/or

(i) a disease, disorder or condition of the endocrine system; and/or

(j) a disease, disorder or condition of the central nervous system (CNS); and/or

(k) a disease, disorder or condition selected from the group consisting of constitutive inflammation including the cryopyrin-associated periodic syndromes (CAPS): Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease (NOMID); including autoinflammatory diseases: familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammation,

antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD); Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO); autoimmune diseases including multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren's syndrome and Schnitzler syndrome; respiratory diseases including chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis and cystic fibrosis; central nervous system diseases including Parkinson's disease, Alzheimer's disease, motor neuron disease, Huntington's disease, cerebral malaria and brain injury from pneumococcal meningitis; metabolic diseases including Type 2 diabetes, atherosclerosis, obesity, gout, pseudo-gout; ocular diseases including those of the ocular epithelium, age-related macular degeneration (AMD), corneal infection, uveitis and dry eye; kidney disease including chronic kidney disease, oxalate nephropathy and diabetic nephropathy; liver disease including non-alcoholic steatohepatitis and alcoholic liver disease; inflammatory reactions in skin including contact hypersensitivity and sunburn; inflammatory reactions in the joints including osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis; viral infections including alpha virus including Chikungunya and Ross River, and flavivirus including Dengue and Zika viruses, flu, HIV; hidradenitis suppurativa (HS) and other cyst-causing skin diseases; cancers including lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia; polymyositis; stroke; myocardial infarction; Graft versus Host Disease; hypertension; colitis; helminth infection; bacterial infection; abdominal aortic aneurism; wound healing; depression, psychological stress; pericarditis including Dressler's syndrome; ischaemia reperfusion injury; and any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.