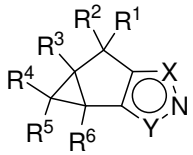
cancerous cell lines (Munro, S. *et al.* (1993) *Nature* 365:61-65; and as reviewed in Pacher, P. *et al.* (2006) *Pharmacol. Rev*. 58(3): 389-462). As such, CB_1 is believed to be primarily responsible for mediating the psychotropic effects of cannabinoids on the body, whereas CB_2 is believed to be primarily responsible for most of their non-neural effects.

The texts of the references cited in this disclosure are herein incorporated by reference in their entireties. In the event that a definition of a term as incorporated by reference differs from the meaning defined herein, then the meaning provided herein is intended.

SUMMARY ~~OF THE INVENTION~~

One ~~aspect~~example of the present ~~invention~~disclosure encompasses certain pyrazole derivatives selected from compounds of Formula **Ia** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ia

wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from: H and C_1-C_6 alkyl;

X is NR^7 and Y is $CC(O)N(R^8)R^9$; or

X is $CC(O)N(R^8)R^9$ and Y is NR^7;

R^7 is $-R^{10}-R^{11}-R^{12}-R^{13}$; wherein:

R^{10} is selected from: C_1-C_6 alkylene, heteroarylene, and heterocyclylene; or R^{10} is absent;

R^{11} is selected from: -C(O)NH- and C_1-C_6 alkylene; or R^{11} is absent;

R^{12} is C_1-C_6 alkylene; or R^{12} is absent; and

R^{13} is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylsulfonyl, amino, C_3-C_7 cycloalkyl, cyano, C_2-C_8 dialkylamino, C_1-C_6 haloalkyl, halogen, and hydroxyl;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-

C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent;

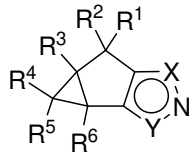
R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, amino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: Carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

One ~~aspect~~example of the present ~~invention~~disclosure encompasses certain pyrazole derivatives selected from compounds of Formula **Ia** and pharmaceutically acceptable salts, solvates, and hydrates thereof:



Ia

wherein:

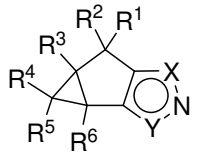
R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from: H and C_1-C_6 alkyl;

X is NR^7 and Y is $CC(O)N(R^8)R^9$; or

X is $CC(O)N(R^8)R^9$ and Y is NR^7;

wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

In one aspect, the present disclosure refers to a compound selected from compounds of Formula **Ia** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ia

wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from: H and C_1-C_6 alkyl;

X is NR^7 and Y is $CC(O)N(R^8)R^9$; or

X is $CC(O)N(R^8)R^9$ and Y is NR^7;

R^7 is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylsulfonyl, amino, C_3-C_7 cycloalkyl, cyano, C_2-C_8 dialkylamino, C_1-C_6 haloalkyl, halogen, and hydroxyl;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent;

R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, amino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: Carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl;

wherein:

each aryl is a ring system containing 6 to 10 carbon atoms, that may contain a single ring or two fused rings, and wherein at least one ring is aromatic;

each heteroaryl is a ring system containing 5 to 14 ring atoms, that may contain a single ring, two fused rings or three fused rings, and wherein at least one ring is aromatic and at least one ring atom is a heteroatom selected from O, S, and N, wherein N is optionally substituted with H, C_1-C_4 acyl, C_1-C_4 alkyl, or oxide;

each heterocyclyl is a non-aromatic ring radical containing 3 to 8 ring atoms, wherein one, two or three ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens;

each heterobicyclyl is a radical comprising two fused or bridged, non-aromatic rings containing 5 to 11 ring atoms wherein one, two, three or four ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens;

each heteroarylene is an aromatic ring di-radical containing 5 to 14 ring atoms that may be a single ring, two fused rings or three fused rings, wherein at least one aromatic ring atom is a heteroatom selected from O, S, and N, wherein N is optionally substituted with H, C_1-C_4 acyl, C_1-C_4 alkyl, or oxide; and

each heterocyclylene is a non-aromatic ring di-radical containing 3 to 8 ring atoms, wherein one, two, or three ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens.

One ~~aspect~~example of the present ~~invention~~disclosure relates to processes for preparing pharmaceutical compositions comprising admixing a compound of the present ~~invention~~disclosure and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a process for preparing a pharmaceutical composition comprising admixing any one of the compounds described herein and a pharmaceutically acceptable carrier.

One ~~aspect~~example of the present ~~invention~~disclosure relates to pharmaceutical compositions comprising a compound of the present ~~invention~~disclosure and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the compounds described herein and a pharmaceutically acceptable carrier.

One ~~aspect~~example of the present ~~invention~~disclosure relates to method for the treatment of a cannabinoid receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of a CB_2 receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of a CB_1/CB_2 receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of bone and joint pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of bone pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of joint pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of pain associated with osteoarthritis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of osteoarthritis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of osteoporosis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of hyperalgesia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of allodynia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of inflammatory pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of inflammatory hyperalgesia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of neuropathic pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of neuropathic hyperalgesia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of acute nociception in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of muscle pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of dental pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of migraine and other headache pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of pain that occurs as an adverse effect of therapeutics in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of pain associated with a disorder selected from: cancer, multiple sclerosis, allergic reactions, nephritic syndrome, scleroderma, thyroiditis, diabetic neuropathy, fibromyalgia, HIV related-neuropathy, sciatica, and autoimmune conditions, in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of multiple sclerosis-associated spasticity in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of autoimmune disorders in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of an autoimmune disorder selected from the group consisting of: multiple sclerosis, Guillan-Barré syndrome, polyradiculoneuropathy, chronic inflammatory demyelination, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis, and reactive arthritis, in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of allergic reactions in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of an allergic reaction associated with a disorder selected from: atopic dermatitis, pruritis, urticaria, asthma, conjunctivitis, allergic rhinitis, and anaphylaxis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of CNS inflammation in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of CNS inflammation associated with a disorder selected from: Alzheimer's disease, stroke, dementia, amyotrophic lateral sclerosis, and human immunodeficiency virus, in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of atherosclerosis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of undesired immune cell activity and inflammation associated with a disorder selected from: osteoarthritis, anaphylaxis, Behcet's disease, graft rejection, vasculitis, gout, spondylitis, viral disease, bacterial disease, lupus, inflammatory bowel disease, autoimmune hepatitis, and type 1 diabetes mellitus, in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of age-related macular degeneration in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of cough in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of leukemia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of lymphoma in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of CNS tumors in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of prostate cancer in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of Alzheimer's disease in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of stroke-induced damage in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of dementia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

One ~~aspect~~example of the present ~~invention~~disclosure relates to a method for the treatment of amyotrophic lateral sclerosis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

A method for the treatment of Parkinson's disease in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present ~~invention~~disclosure.

In one aspect, the present disclosure refers to use of any one of the compounds described herein, in the manufacture of a medicament for modulating the activity of a cannabinoid CB_2 receptor.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of a cannabinoid receptor-mediated disorder. In one aspect, the present disclosure refers to use of any one of the compounds described herein, or a pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of a cannabinoid receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of a CB_2 receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of a CB_1/CB_2 receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of pain. In one aspect, the present disclosure refers to use of any one of the compounds described herein, or a pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of bone and joint pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of bone pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of joint pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of pain associated with osteoarthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of osteoarthritis. In one aspect, the present disclosure refers to use of any one of the compounds described herein, or a pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of osteoarthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of osteoporosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of allodynia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of inflammatory pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of inflammatory hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of neuropathic pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of neuropathic hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of acute nociception.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of muscle pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of dental pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of migraine and other headache pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of pain that occurs as an adverse effect of therapeutics.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of pain associated with a disorder selected from: cancer, multiple sclerosis, allergic reactions, nephritic syndrome, scleroderma, thyroiditis, diabetic neuropathy, fibromyalgia, HIV related-neuropathy, sciatica, and autoimmune conditions.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of multiple sclerosis-associated spasticity.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of autoimmune disorders.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of an autoimmune disorder selected from the group consisting of: multiple sclerosis, Guillan-Barré syndrome, polyradiculoneuropathy, chronic inflammatory demyelination, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis, and reactive arthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of allergic reactions.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of an allergic reaction associated with a disorder selected from: atopic dermatitis, pruritis, urticaria, asthma, conjunctivitis, allergic rhinitis, and anaphylaxis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of CNS inflammation.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of CNS inflammation associated with a disorder selected from: Alzheimer's disease, stroke, dementia, amyotrophic lateral sclerosis, and human immunodeficiency virus.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of atherosclerosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of undesired immune cell activity and inflammation associated with a disorder selected from: osteoarthritis, anaphylaxis, Behcet's disease, graft rejection, vasculitis, gout, spondylitis, viral disease, bacterial disease, lupus, inflammatory bowel disease, autoimmune hepatitis, and type 1 diabetes mellitus.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of age-related macular degeneration.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of cough.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of leukemia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of lymphoma.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of CNS tumors.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of prostate cancer.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of Alzheimer's disease.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of stroke-induced damage.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of dementia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of Parkinson's disease.

In one aspect, the present disclosure refers to any one of the compounds described herein, for use in modulating the activity of a cannabinoid CB_2 receptor.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of a cannabinoid receptor-mediated disorder. In one aspect, the present disclosure refers to any one of the compounds described herein, or a pharmaceutical composition described herein, for use in the treatment of a cannabinoid receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of the human or animal body by therapy.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of a CB_2 receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of a CB_1/CB_2 receptor-mediated disorder.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of pain. In one aspect, the present disclosure refers to any one of the compounds described herein, or a pharmaceutical composition described herein, for use in the treatment of pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of bone and joint pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of bone pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of joint pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of pain associated with osteoarthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of osteoarthritis. In one aspect, the present disclosure refers to any one of the compounds described herein, or a pharmaceutical composition described herein, for use in the treatment of osteoarthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of osteoporosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of allodynia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of inflammatory pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of inflammatory hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of neuropathic pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of neuropathic hyperalgesia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of acute nociception.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of muscle pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of dental pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of migraine and other headache pain.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of pain that occurs as an adverse effect of therapeutics.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of pain associated with a disorder selected from: cancer, multiple sclerosis, allergic reactions, nephritic syndrome, scleroderma, thyroiditis, diabetic neuropathy, fibromyalgia, HIV related-neuropathy, sciatica, and autoimmune conditions.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of multiple sclerosis-associated spasticity.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of autoimmune disorders.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of an autoimmune disorder selected from the group consisting of: multiple sclerosis, Guillan-Barré syndrome, polyradiculoneuropathy, chronic inflammatory demyelination, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis, and reactive arthritis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of allergic reactions.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of an allergic reaction associated with a disorder selected from: atopic dermatitis, pruritis, urticaria, asthma, conjunctivitis, allergic rhinitis, and anaphylaxis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of CNS inflammation.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of CNS inflammation associated with a disorder selected from: Alzheimer's disease, stroke, dementia, amyotrophic lateral sclerosis, and human immunodeficiency virus.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of atherosclerosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of undesired immune cell activity and inflammation associated with a disorder selected from: osteoarthritis, anaphylaxis, Behcet's disease, graft rejection,

vasculitis, gout, spondylitis, viral disease, bacterial disease, lupus, inflammatory bowel disease, autoimmune hepatitis, and type 1 diabetes mellitus.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of age-related macular degeneration.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of cough.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of leukemia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of lymphoma.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of CNS tumors.

One ~~aspect~~example of the present ~~invention~~disclosure relates to the use of a compound of the present ~~invention~~disclosure in the manufacture of a medicament for the treatment of prostate cancer.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of Alzheimer's disease.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of stroke-induced damage.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of dementia.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of amyotrophic lateral sclerosis.

One ~~aspect~~example of the present ~~invention~~disclosure relates to compounds of the present ~~invention~~disclosure for use in a method of treatment of Parkinson's disease.

These and other ~~aspect~~examples of the ~~invention~~disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of Compound **493** in the FCA-induced hyperalgesia model of inflammatory pain in rats at 1 h post dosing. See Example **7**.

Figure 2 shows the effect of Compound **493** in the monosodium iodoacetate (MIA) model of osteoarthritis in rats at 1 h post dosing. See Example **5**.

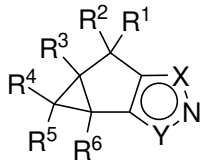
Figure 3 shows the effect of 10 mg/kg of Compound **493** on paclitaxel-induced allodynia in rats. See Example **8**.

Figure 4 shows the effect of Compound **493** on the skin incision model of post-operative pain in rats. See Example **6**.

CLAIMS

What is claimed is:

1. A compound selected from compounds of Formula **Ia** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ia

wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from: H and C_1-C_6 alkyl;

X is NR^7 and Y is $CC(O)N(R^8)R^9$; or

X is $CC(O)N(R^8)R^9$ and Y is NR^7;

R^7 ~~is -R^{10}-R^{11}-R^{12}-R^{13}; wherein:~~

~~R^{10} is selected from: C_1-C_6 alkylene, heteroarylene, and heterocyclylene; or R^{10} is absent;~~

~~R^{11} is selected from: -C(O)NH- and C_1-C_6 alkylene; or R^{11} is absent;~~

~~R^{12} is C_1-C_6 alkylene; or R^{12} is absent; and~~

~~R^{13}~~ is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylsulfonyl, amino, C_3-C_7 cycloalkyl, cyano, C_2-C_8 dialkylamino, C_1-C_6 haloalkyl, halogen, and hydroxyl;

R^8 is -R^{14}-R^{15}-R^{16}-R^{17}; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent;

R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, amino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: Carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl~~.~~;

wherein:

each aryl is a ring system containing 6 to 10 carbon atoms, that may contain a single ring or two fused rings, and wherein at least one ring is aromatic;

each heteroaryl is a ring system containing 5 to 14 ring atoms, that may contain a single ring, two fused rings or three fused rings, and wherein at least one ring is aromatic and at least one ring atom is a heteroatom selected from O, S, and N, wherein N is optionally substituted with H, C_1-C_4 acyl, C_1-C_4 alkyl, or oxide;

each heterocyclyl is a non-aromatic ring radical containing 3 to 8 ring atoms, wherein one, two or three ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens;

each heterobicyclyl is a radical comprising two fused or bridged, non-aromatic rings containing 5 to 11 ring atoms wherein one, two, three or four ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens;

each heteroarylene is an aromatic ring di-radical containing 5 to 14 ring atoms that may be a single ring, two fused rings or three fused rings, wherein at least one aromatic ring atom is a

heteroatom selected from O, S, and N, wherein N is optionally substituted with H, C_1-C_4 acyl, C_1-C_4 alkyl, or oxide; and

each heterocyclylene is a non-aromatic ring di-radical containing 3 to 8 ring atoms, wherein one, two, or three ring atoms are heteroatoms selected from O, S, and N, wherein N is substituted with H, C_1-C_4 acyl, or C_1-C_4 alkyl, and S is optionally substituted with one or two oxygens.

2. The compound according to claim 1, wherein:

R^{15} is selected from: -C(O)NH-, -C(O)-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl.

3. The compound according to claim 1 or 2, wherein:

R^1 and R^6 are each independently selected from: H~~,~~ and C_1-C_6 alkyl; and

R^2, R^3, R^4, and R^5 are each H.

4. The compound according to claim 1 or 2, wherein R^1, R^2, R^3, R^4, R^5, and R^6 are each H.

5. The compound according to any one of claims 1 to 4, wherein X is NR^7 and Y is $CC(O)N(R^8)R^9$.

6. The compound according to any one of claims 1 to 4, wherein X is $CC(O)N(R^8)R^9$ and Y is NR^7.

~~7. The compound according to any one of claims 1 to 6, wherein R^{10} is selected from: C_1-C_6 alkylene, heteroarylene, and heterocyclylene.~~

~~8. The compound according to any one of claims 1 to 6, wherein R^{10} is absent.~~

~~9. The compound according to any one of claims 1 to 8, wherein R^{11} is selected from: C(O)NH and C_1-C_6 alkylene.~~

~~10. The compound according to any one of claims 1 to 8, wherein R^{11} is absent.~~

~~11. The compound according to any one of claims 1 to 10, wherein R^{12} is C_1-C_6 alkylene.~~

~~12. The compound according to any one of claims 1 to 10, wherein R^{12} is absent.~~

~~13.~~7. The compound according to any one of claims 1 to ~~12~~6, wherein ~~R~~^{13}-R^7 is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: fluoro, bromo, chloro, iodo, methoxy, cyano, methyl, *tert*-butyl, isopropyl, hydroxyl, ethyl, heptafluoropropyl, cyclobutyl, trifluoromethyl, cyclopropyl, dimethylamino, methoxy, ethoxy, methylamino, propyl, amino, and methanesulfonyl.

~~14.~~8. The compound according to any one of claims 1 to ~~12~~6, wherein ~~R~~^{13}-R^7 is selected from: 2,4-difluoro-phenyl, 2,4-dichloro-phenyl, 2-fluoro-4-methanesulfonyl-phenyl, 2,6-difluoro-phenyl, 2,5-difluoro-phenyl, 4-methoxy-phenyl, 4-cyano-phenyl, 4-fluoro-phenyl, phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, *o*-tolyl, *tert*-butyl, isopropyl, 2,2-dimethylpropyl, hydroxyl, 2-hydroxy-2-methylpropyl, 1-oxo-hexahydro-1λ^4-thiopyran-4-yl, 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl, tetrahydrothiopyran-4-yl, morpholin-4-yl, tetrahydro-pyran-4-yl, 1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, pyrazin-2-yl, 5-ethyl-pyrazin-2-yl, 5-hydroxy-pyrazin-2-yl, 5-isopropyl-pyrazin-2-yl, 5-heptafluoropropyl-pyrazin-2-yl, 5-cyclobutyl-pyrazin-2-yl, 5-methyl-pyrazin-2-yl, 6-ethyl-pyrazin-2-yl, 5-trifluoromethyl-pyrazin-2-yl, cyclopropyl, 5-cyclopropyl-pyrazin-2-yl, 6-chloro-pyrazin-2-yl, 5-dimethylamino-pyrazin-2-yl, 4-cyano-phenyl, 6-methoxy-pyridazin-3-yl, 6-chloro-pyridazin-3-yl, pyrimidin-5-yl, 6-dimethylamino-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 2-pyrimidin-4-yl, 5-bromo-pyrazin-2-yl, 5-hydroxy-pyrazin-2-yl, 5-methoxy-pyrazin-2-yl, 5-ethoxypyrazin-2-yl, 5-methylamino-pyrazin-2-yl, 5-bromo-pyridin-2-yl, pyridin-3-yl, 5-trifluoromethyl-pyridin-2-yl, 5-isopropyl-pyridin-2-yl, 5-isopropyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 5-ethyl-pyridin-2-yl, 5-methoxy-pyridin-2-yl, 4-trifluoromethyl-pyridin-2-yl, 5-

cyano-pyridin-2-yl, 5-dimethylamino-pyridin-2-yl, 4-methyl-pyridin-2-yl, 5-chloro-4-methyl-pyridin-2-yl, 5-chloro-4-trifluoromethyl-pyridin-2-yl, 4-trifluoromethyl-pyridin-2-yl, 3-fluoro-pyridin-2-yl, 6-methyl-4-trifluoromethyl-pyridin-2-yl, 3-methyl-pyridin-2-yl, 5-propyl-pyridin-2-yl, 5-cyclopropyl-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3,5-difluoro-pyridin-2-yl, 6-bromo-pyridin-3-yl, 5-bromo-pyridin-3-yl, 5,6-difluoro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 3-fluoro-pyridin-4-yl, 5-cyano-pyridin-3-yl, pyridin-4-yl, 2-chloro-pyridin-4-yl, 2-methoxy-pyridin-4-yl, 6-methyl-pyridin-3-yl, *m*-tolyl, thiazol-2-yl, cyclopentyl, 4-amino-pyridin-2-yl, 4-methoxy-pyridin-2-yl, 4-chloro-pyridin-2-yl, 4-fluoro-pyridin-2-yl, 4-cyclopropyl-pyridin-2-yl, 4-bromo-pyridin-2-yl, 4-methanesulfonyl-pyridin-2-yl, 4-cyano-pyridin-2-yl, hydroxymethyl, 4-oxy-pyrazin-2-yl, 3-methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 5-chloro-3-fluoro-pyridin-2-yl, 3-fluoro-5-methoxy-pyridin-2-yl, 2-chloro-4-fluoro-phenyl, 6-fluoro-pyridin-3-yl, 6-cyano-pyridin-3-yl, 4-iodo-pyridin-2-yl, 1-oxy-pyridin-3-yl, and 4-hydroxy-pyridin-2-yl.

~~15.~~9. The compound according to any one of claims 1 to 6, wherein R^7 is selected from: 2,4-difluoro-phenyl, 5-bromo-pyridin-2-yl, 4-cyano-phenyl, pyridin-3-yl, pyridin-2-yl, 5-thiazol-2-yl-pyridin-2-yl, 5-trifluoromethyl-pyridin-2-yl, 5-*o*-tolyl-pyridin-2-yl, 5-dimethylamino-pyrazin-2-yl, 2,4-dichloro-phenyl, 5-isopropyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 5-(4-methoxy-phenyl)-pyridin-2-yl, 2-fluoro-4-methanesulfonyl-phenyl, 2-fluoro-phenyl, 5-chloro-pyridin-2-yl, 5-bromo-pyridin-3-yl, *tert*-butyl, 2-methoxy-pyridin-4-yl, 2,2-dimethyl-propyl, tetrahydro-pyran-4-ylmethyl, phenyl, 4-trifluoromethyl-pyridin-2-yl, 6-chloro-pyrazin-2-yl, 1-oxo-hexahydro-1□^{4}-thiopyran-4-yl, 5-morpholin-4-yl-pyridin-2-yl, 6-bromo-pyridin-3-yl, 5-methoxy-pyridin-2-yl, 5,6-difluoro-pyridin-3-yl, 6-methoxy-pyridazin-3-yl, 2-chloro-pyridin-4-yl, 5-cyclopropyl-pyrazin-2-yl, 1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 1-benzyl-piperidin-4-yl, 6-cyano-pyrazin-2-yl, 2-hydroxy-2-methyl-propyl, 4-fluoro-phenyl, 5-ethyl-pyridin-2-yl, isopropyl, 5-phenyl-pyridin-2-yl, pyridin-4-yl, 2,5-difluoro-phenyl, 3-fluoro-phenyl, pyrimidin-4-yl, 2-(tetrahydro-pyran-4-yl)-ethyl, 3,5-difluoro-pyridin-2-yl, pyrazin-2-yl, tetrahydro-thiopyran-4-yl, 5-*p*-tolyl-pyridin-2-yl, 4-methoxy-phenyl, 2-morpholin-4-yl-ethyl, 5-cyano-pyridin-2-yl, 5-cyano-pyrazin-2-yl, 6'-methyl-[3,3']bipyridinyl-6-yl, 6-chloro-pyridazin-3-yl, 5-fluoro-pyridin-2-yl, 5-ethyl-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 5-dimethylamino-pyridin-2-yl, 1-(4-fluoro-phenyl)-1-methyl-ethyl, 5-pyrimidin-5-yl-pyridin-2-yl, 4-methyl-pyridin-2-yl, 5-methoxy-pyrazin-2-yl, 5-propyl-pyridin-2-yl, 6-chloro-pyridin-3-yl, 5-*m*-tolyl-pyridin-2-yl, 5-hydroxy-pyrazin-2-yl, cyclopropyl-pyridin-2-yl, 2,6-difluoro-phenyl, 3-fluoro-pyridin-4-yl, 5-isopropyl-pyrazin-2-yl, 5-bromo-pyrazin-2-yl, 5-cyclopentyl-pyridin-2-yl, *o*-tolyl, 4-fluoro-benzyl, 3-methyl-pyridin-2-yl, 6-methyl-4-trifluoromethyl-pyridin-2-yl, 6-dimethylamino-pyrazin-2-yl, 1,1-dioxo-hexahydro-

1λ^6-thiopyran-4-yl, 5-(4-fluoro-phenyl)-pyridin-2-yl, 5-cyclopropyl-pyridin-2-yl, 6-ethyl-pyrazin-2-yl, 5-methylamino-pyrazin-2-yl, 5-methyl-pyrazin-2-yl, 3-fluoro-pyridin-2-yl, 5-cyclobutyl-pyrazin-2-yl, 5-ethoxy-pyrazin-2-yl, 5-trifluoromethyl-pyrazin-2-yl, 5-cyano-pyridin-3-yl, 5-cyclopropylmethyl-pyrazin-2-yl, 5-pentafluoroethyl-pyrazin-2-yl, 5-heptafluoropropyl-pyrazin-2-yl, 5-chloro-4-methyl-pyridin-2-yl, 5-chloro-4-trifluoromethyl-pyridin-2-yl, 4-bromo-pyridin-2-yl, 4-chloro-pyridin-2-yl, 4-fluoro-pyridin-2-yl, 4-oxy-pyrazin-2-yl, 4-cyclopropyl-pyridin-2-yl, 4-cyano-pyridin-2-yl, 4-methanesulfonyl-pyridin-2-yl, 4-methoxy-pyridin-2-yl, piperidin-4-yl**,** tetrahydro-pyran-4-yl, 3-methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 5-chloro-3-fluoro-pyridin-2-yl, 3-fluoro-5-methoxy-pyridin-2-yl, 2-chloro-4-fluoro-phenyl, 6-fluoro-pyridin-3-yl, 6-cyano-pyridin-3-yl, 3-hydroxy-3-methyl-butyl, 4-iodo-pyridin-2-yl, 1-oxy-pyridin-3-yl, 4-*tert*-butylcarbamoyl-pyridin-2-yl, and 4-hydroxy-pyridin-2-yl.

~~16.~~10. The compound according to any one of claims 1 to ~~15~~9, wherein R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl.

~~17.~~11. The compound according to any one of claims 1 to ~~15~~9, wherein R^{14} is selected from: methylene, ethylene, 1,1-cyclopropylene, 1,1-dimethyl-methylene, 1,1-cyclobutylene, *tert*-butyl-methylene, 1-methyl-4,4-piperidinylene, 4,4-tetrahydro-2*H*-pyranylene, methyl-methylene, 1,1-cyclohexylene, 1,2-cyclohexylene, 1,1-dimethyl-ethylene, 1-*tert*-butyl-ethylene, 1-ethyl-ethylene, 1-methyl-ethylene, 1-(tetrahydro-2*H*-pyran-4-yl)-ethylene, isopropyl-methylene, 1,1-cyclopentylene, benzyl-methylene, 4,4-cyclopent-1-enylene, 1,1-dioxo-hexahydro-1λ^6-4,4-thiopyranylene, 1-*tert*-butoxycarbonyl-4,4-piperidinylene, 1-(pyridin-4-yl)-ethylene, 1-(pyridin-3-yl)-ethylene, 1-(pyridin-2-yl)-ethylene, 1-(4-fluoro-phenyl)-ethylene, 1-hydroxymethyl-1-methyl-ethylene, 1-carboxy-1-methyl-ethylene, 1-methoxymethyl-ethylene, 1-hydroxymethyl-ethylene, 1-(1-hydroxyethyl)-ethylene, 1,1-dimethyl-ethylene, 1-(tetrahydro-furan-3-yl)-ethylene, phenyl-methylene, 1-(3*H*-imidazol-4-ylmethyl)-ethylene, 1-(4-hydroxy-phenyl)-ethylene, benzyl-ethylene, (1-hydroxymethyl-2-methyl)-ethylene, 1-isopropyl-ethylene, pyridin-2-yl-methylene, 1,1-dimethyl-propylene, 2-hydroxy-propylene, (1-isobutyl-pyrrolidin-3-yl)-methylene, 1,3-azetidinylene, 1,3-pyrrolidinylene, 1,3-piperidinylene, 1,4-piperidinylene, 2,4-thiazolylene, 3,4-

pyridinylene, 2,4-pyridinylene, 2,5-pyridinylene, -SO_2-, 2,5-pyridinylene, 1-cyclopropyl-ethylene, 1-(*sec*-butyl)-ethylene, 1-hydroxymethyl-1-ethyl-ethylene, 1-isopropyl-ethylene, 1-(2,2,2-trifluoroethyl)-ethylene, (2-fluoropropan-2-yl)-methylene, (1,1,1,3,3,3-hexafluoropropan-2-yl)-methylene, 1-(2-fluoropropan-2-yl)-ethylene, (2,2,2-trifluoroethyl)-methylene, 1,1-di(fluoromethyl)-ethylene, (hydroxymethyl)(methyl)methylene, (hydroxymethyl)(methyl)methylene, 3,3-oxetanylene, and 1-hydroxymethyl-1-isopropyl-ethylene.

~~18.~~12. The compound according to any one of claims 1 to ~~15~~9, wherein R^{14} is absent.

~~19.~~13. The compound according to any one of claims 1 to ~~18~~12, wherein R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl.

~~20.~~14. The compound according to any one of claims 1 to ~~18~~12, wherein R^{15} is selected from: 1,3-pyrrolidinylene, 1,4-piperidinylene, 2,6-pyridinylene, 1,3-azetidinylene, -C(O)NH-, -C(O)-, -C(O)O-, 1,2-pyrrolidinylene, 2,4-morpholinylene, ethylene, methylene, 1,1-cyclopentylene, 4,4-tetrahydro-2*H*-pyranylene, 3,3-tetrahydro-thiophenylene, 1,1-cyclopropylene, 1-methyl-4,4-piperidinylene, and 1-oxo-tetrahydro-1λ^4-3,3-thiophenylene.

~~21.~~15. The compound according to any one of claims 1 to ~~18~~12, wherein R^{15} is absent.

~~22.~~16. The compound according to any one of claims 1 to ~~21~~15, wherein R^{16} is C_1-C_6 alkylene.

~~23.~~17. The compound according to any one of claims 1 to ~~21~~15, wherein R^{16} is absent.

~~24.~~18. The compound according to any one of claims 1 to ~~23~~17, wherein R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6

alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl.

~~25.~~19. The compound according to any one of claims 1 to ~~23~~17, wherein R^{17} is selected from: H, amino, 1-*tert*-butoxycarbonylamino, morpholin-4-yl, 4-methyl-piperidin-1-yl, piperidin-4-yl, 1-*tert*-butoxycarbonyl-piperidin-3-yl, tetrahydro-thiopyran-4-yl, 1-oxo-hexahydro-1λ^4-thiopyran-4-yl, tetrahydro-pyran-4-yl, pyrrolidin-1-yl, 1-*tert*-butoxycarbonyl-azetidin-3-yl, 2,6-dimethyl-morpholin-4-yl, piperidin-1-yl, 1-*tert*-butoxycarbonyl-piperidin-4-yl, 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl, tetrahydro-furan-2-yl, 1-ethyl-pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, morpholin-2-yl, 1-methyl-piperidin-2-yl, 1-methyl-piperidin-4-yl, 4-hydroxy-1-methyl-piperidin-4-yl, thiomorpholin-4-yl, tetrahydro-furan-3-yl, 1-*tert*-butoxycarbonyl-pyrrolidin-4-yl, 1,2,2,6,6-pentamethyl-piperidin-4-yl, 1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 4-methyl-morpholin-2-yl, 4-*tert*-butoxycarbonyl -morpholin-2-yl, 1-isopropyl-piperidin-4-yl, 4-hydroxy-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 3-methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, phenyl, 2-hydroxy-indan-1-yl, indan-1-yl, cyclopentyl, 2-hydroxy-cyclopentyl, cyclobutyl, 2-hydroxy-cyclohexyl, 1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-yl, 1-aza-bicyclo[2.2.2]oct-3-yl, 9-methyl-9-aza-bicyclo[3.3.1]non-1-yl, 3-azepan-1-yl, 2-fluoro-phenyl, 2-chloro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 3-fluoro-phenyl, 5-fluoro-2-methoxy-phenyl, 2-fluoro-4-methanesulfonyl-phenyl, 4-carboxy-2-fluoro-phenyl, 2,5-difluoro-phenyl, *m*-tolyl, *o*-tolyl, 2,5-dimethyl-phenyl, 2,3-dimethyl-phenyl, 4-hydroxy-3-methoxy-phenyl, 2,4-dimethoxy-phenyl, 2,3-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 4-methoxy-phenyl, 3-methoxy-phenyl, 2-methoxy-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 2-hydroxy-phenyl, 5-fluoro-2-hydroxy-phenyl, 3-trifluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-difluoromethoxy-phenyl, 4-fluoro-phenoxy, 2-dimethylamino-phenyl, 4-dimethylamino-phenyl, 6-fluoro-4*H*-benzo[1,3]dioxin-8-yl, benzo[1,3]dioxol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, 2,6-dimethyl-pyrimidin-4-yl, pyridazin-3-yl, 5-methyl-pyrazin-2-yl, 6-methoxy-pyrimidin-4-yl, pyrazin-2-yl, 3,5-dimethyl-pyrazin-2-yl, 5-fluoro-2-oxo-2,3-dihydro-pyrimidin-4-yl, hydroxyl, methoxycarbonyl, ethoxycarbonyl, carboxy, 1-piperidin-1-yl, carboxamide, methoxy, trifluoromethyl, methyl, *tert*-butyl, diethylamino, dimethylamino, cyano, *tert*-butylamino, cyclopropyl, pyridin-3-yloxy, 1*H*-tetrazol-5-yl, 5-methyl-[1,2,4]oxadiazol-3-yl, phosphonooxy, cyclobutylamino, phenylamino, 1-*tert*-butyl-3-methylureido, 3-methyl-1-phenylureido, *N*-*tert*-butylmethylsulfonamido, 1-cyclobutyl-3-methylureido, methylcarbamoyl, 5-hydroxy-1*H*-indol-3-yl, 1*H*-benzoimidazol-2-yl, 5,7-dimethyl-pyrazolo[1,5-a]pyrimidin-2-yl, 1*H*-benzoimidazol-2-yl,

2-(*tert*-butoxycarbonyl)- 3,4-dihydro-1*H*-isoquinoline-2-yl, quinolin-3-yl, quinolin-4-yl, 2-methyl-quinolin-4-yl, benzooxazol-2-yl, 1-methyl-1,2,3,4-tetrahydro-quinolin-7-yl, 2,3-dihydro-benzofuran-3-yl, benzothiazol-2-yl, 1,4-dimethyl-1*H*-pyrrol-2-yl, 3-methyl-3*H*-imidazol-4-yl, 1*H*-imidazol-4-yl, 5-hydroxy-1*H*-pyrazol-3-yl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyridin-2-yl-thiazol-2-yl, 5-methyl-thiazol-2-yl, oxazol-4-yl, 4-phenyl-thiazol-2-yl, 5-*tert*-butyl-isoxazol-3-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 3-hydroxy-pyridin-2-yl, 6-hydroxy-pyridin-3-yl, 3-hydroxy-pyridin-4-yl, 4-hydroxy-pyridin-2-yl, 6-hydroxy-pyridin-2-yl, 2-hydroxy-pyridin-3-yl, 2-methoxy-pyridin-3-yl, 5-methoxy-pyridin-2-yl, 4-methoxy-pyridin-2-yl, 2-methoxy-pyridin-4-yl, 6-methoxy-pyridin-2-yl, 6-methoxy-pyridin-3-yl, 3-fluoro-pyridin-2-yl, 2-fluoro-pyridin-3-yl, 6-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 3-fluoro-pyridin-4-yl, 3-methyl-pyridin-2-yl, 3-methyl-pyridin-4-yl, 6-methyl-pyridin-2-yl, 4-methyl-pyridin-2-yl, 6-methyl-pyridin-3-yl, 2-methyl-pyridin-3-yl, 5-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-3-yl, 4-trifluoromethyl-pyridin-2-yl, 3-chloro-5-trifluoromethyl-pyridin-2-yl, 4,6-dimethyl-pyridin-2-yl, 4,6-dimethyl-pyridin-2-yl, 3-chloro-5-methyl-pyridin-2-yl, 6-cyano-pyridin-3-yl, 3-cyano-5-methyl-pyridin-2-yl, 3-cyano-5-methyl-pyridin-2-yl, 3-chloro-5-methyl-pyridin-2-yl, 2-chloro-pyridin-3-yl, 5-chloro-pyridin-2-yl, 6-chloro-2-methyl-pyridin-3-yl, 6-chloro-pyridin-3-yl, 3-chloro-pyridin-4-yl, 6-bromo-2-methyl-pyridin-3-yl, 5-bromo-3-methyl-pyridin-2-yl, 6-carboxypyridin-2-yl, 6-methanesulfonyl-4-methyl-pyridin-3-yl, 6-methanesulfonyl-4-methyl-pyridin-3-yl, 6-methanesulfonyl-2-methyl-pyridin-3-yl, 6-methanesulfonyl-pyridin-3-yl, 2,6-dimethoxy-pyridin-3-yl, 5-fluoro-1-oxy-pyridin-2-yl, 1-oxy-pyridin-2-yl, 6-pyrrolidin-1-yl-pyridin-2-ylmethyl, 5-(1-methyl-pyrrolidin-2-yl)-pyridin-2-yl, 6-morpholin-4-yl-pyridin-2-yl, 6-morpholin-4-yl-pyridin-3-yl, ethynyl, *tert*-butyl(methyl)amino, 2,2,2-trifluoroethyl, *N*-cyclobutylmethylsulfonamido, *N*-phenylmethylsulfonamido, hydroxy(methyl)amino, methoxy(methyl)amino, azetidin-1-yl, *tert*-butoxy, fluoromethyl, 2,2,2-trifluoroethylamino, and (1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)amino.

~~26.~~20. The compound according to any one of claims 1 to ~~15~~9, wherein R^8 is selected from: H, 2-methyl-2-morpholin-4-yl-propyl, 1-hydroxymethyl-2,2-dimethyl-propyl, 2-(*tert*-butoxycarbonylamino)cyclohexyl, 1-phenyl-cyclopropyl, 5-trifluoromethyl-pyridin-2-yl, 1-methyl-1-phenyl-ethyl, 1-(2-methoxy-ethyl)-pyrrolidin-3-ylmethyl, 1-(methoxycarbonyl)cyclopropyl, tetrahydro-pyran-4-ylmethyl, 1-(*tert*-butoxycarbonyl)piperidin-4-yl, 1-(4-fluoro-phenyl)-cyclopropyl, 6-methyl-pyridin-3-ylmethyl, 2-hydroxy-1-phenyl-ethyl, 1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl, 2-hydroxy-1,1-dimethyl-ethyl, 2-(5-hydroxy-1*H*-indol-3-yl)-ethyl, 1-hydroxymethyl-cyclopropyl, 3-chloro-5-methyl-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 1-

(3-fluoro-phenyl)-cyclobutyl, 2-methyl-pyridin-3-yl, 2-hydroxy-1-(tetrahydro-furan-3-yl)-ethyl, 2-(pyridin-3-yloxy)-propyl, carbamoyl-phenyl-methyl, 5-fluoro-2-methoxy-phenyl, 2-methoxy-ethyl, 2,3-dihydroxy-propyl, 1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl, 2-oxo-2-phenyl-ethyl, 1-(3,3,3-trifluoro-propyl)-azetidin-3-yl, 2-hydroxy-1-pyridin-2-yl-ethyl, 3-hydroxy-pyridin-4-yl, 1-methyl-1-pyridin-4-yl-ethyl, 1-hydroxymethyl-2-3*H*-imidazol-4-yl-ethyl, 4-hydroxy-3-methoxy-benzyl, 5-fluoro-2-oxo-2,3-dihydro-pyrimidin-4-yl, 1-(4-fluoro-phenyl)-3-hydroxy-propyl, 1-pyridin-4-yl-cyclopropyl, 2-hydroxy-1-pyridin-3-yl-ethyl, 1,1-dimethyl-2-(4-methyl-piperidin-1-yl)-ethyl, 6-cyano-pyridin-3-yl, 5-fluoro-pyridin-2-yl, 2,5-dimethyl-benzyl, 1-isopropyl-piperidin-4-yl, 2-methoxy-1-methoxymethyl-ethyl, 2,3-dimethyl-benzyl, 1-pyridin-2-yl-ethyl, 6-chloro-pyridin-3-ylmethyl, 3-methyl-pyridin-2-yl, 2-hydroxy-indan-1-yl, 1-hydroxymethyl-cyclobutyl, 2-(4-chloro-phenyl)-1,1-dimethyl-ethyl, 3-hydroxy-pyridin-2-ylmethyl, 3-methyl-pyridin-4-yl, 5-*tert*-butyl-isoxazol-3-yl, 1-(6-methoxy-pyridin-3-yl)-1-methyl-ethyl, 1*H*-benzoimidazol-2-yl, *tert*-butyl, 4-phenyl-thiazol-2-yl, 1-(2-fluoro-phenyl)-cyclobutyl, 2,4-dimethoxy-benzyl, 5-bromo-3-methyl-pyridin-2-yl, 4-benzyl-morpholin-2-ylmethyl, 6-trifluoromethyl-pyridin-3-ylmethyl, tetrahydro-furan-3-yl, pyridin-3-ylmethyl, pyrazin-2-yl, piperidin-4-yl, 1-(6-hydroxy-pyridin-3-yl)-1-methyl-ethyl, 1-methyl-1-pyridin-2-yl-ethyl, 1-hydroxymethyl-cyclopentyl, 1-aza-bicyclo[2.2.2]oct-3-yl, 2-hydroxy-cyclopentyl, 2-hydroxy-1-(hydroxymethyl)-propyl, 1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl, 3,5-dimethoxy-phenyl, 6-fluoro-4*H*-benzo[1,3]dioxin-8-ylmethyl, 4,6-dimethyl-pyridin-2-yl, 1,1-dimethyl-2-morpholin-4-yl-ethyl, 2-hydroxy-cyclohexylmethyl, 1-(4-methoxy-phenyl)-cyclopropyl, 1-ethyl-pyrrolidin-2-ylmethyl, indan-1-yl, pyrimidin-4-yl, 2-fluoro-4-methanesulfonyl-phenyl, 6-hydroxy-pyridin-2-yl, cyclobutyl, 1-(3-methoxy-phenyl)-cyclopropyl, 1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-yl, 2-hydroxy-pyridin-3-yl, 4-difluoromethoxy-benzyl, 1-piperidin-1-yl-cyclopentylmethyl, 3-hydroxy-3-methyl-butyl, 1-(4-fluoro-phenyl)-cyclobutyl, 4-methoxy-benzyl, pyridin-2-yl, 2-hydroxy-2-phenyl-ethyl, 2-hydroxymethyl-2,3-dihydro-indol-1-yl, 3-hydroxy-pyridin-2-yl, 4-dimethylamino-tetrahydro-pyran-4-ylmethyl, 2-(4-fluoro-phenyl)-ethyl, 1-(2-methoxy-ethyl)-piperidin-4-ylmethyl, 2-morpholin-4-yl-ethyl, 1-(*tert*-butoxycarbonyl)-4-carboxypiperidin-4-yl, quinolin-3-yl, 1-morpholin-4-ylmethyl-cyclopentyl, 1,4-dimethyl-1*H*-pyrrol-2-ylmethyl, 2-hydroxy-2-pyridin-2-yl-ethyl, pyridin-3-yl, 2-dimethylamino-benzyl, tetrahydro-thiopyran-4-yl, 1-*m*-tolyl-cyclopropyl, 1-(2-methoxy-ethyl)-piperidin-3-yl, 5-methoxy-pyridin-2-ylmethyl, 2-hydroxy-1-pyridin-4-yl-ethyl, 4-methyl-pyridin-2-yl, 4-carboxy-2-fluorophenyl, 6-methanesulfonyl-pyridin-3-yl, 1-*o*-tolyl-cyclobutyl, 1,1-dimethyl-2-pyrrolidin-1-yl-ethyl, 2,6-dimethoxy-pyridin-3-yl, pyridin-2-yl, 4-hydroxymethyl-tetrahydro-pyran-4-yl, 2-(1*H*-imidazol-4-yl)-ethyl, 3-fluoro-pyridin-4-yl, 1-carbamoyl-2-phenyl-ethyl, oxazol-4-ylmethyl, 6-methoxy-

pyrimidin-4-yl, 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl, 1-methoxy-1-oxo-3-phenylpropan-2-yl, 1-(2-methoxy-ethyl)-pyrrolidin-3-yl, 1-(6-methyl-pyridin-2-yl)-ethyl, 2-hydroxy-1-(4-hydroxy-phenyl)-ethyl, 2-methoxy-pyridin-4-yl, 1-pyridin-2-yl-cyclopropyl, 1-(*tert*-butoxycarbonyl)piperidin-3-yl, 3-methyl-pyridin-2-ylmethyl, 3-fluoro-pyridin-2-yl, 1-pyridin-4-yl-cyclobutyl, 2-carboxy-1-(pyridin-3-yl)ethyl, 2-hydroxy-1-methyl-ethyl, 1-(methoxycarbonyl)cyclohexyl, 3-hydroxymethyl-pyridin-4-yl, 2-hydroxy-1-phenyl-ethyl, 3-dimethylamino-tetrahydro-thiophen-3-ylmethyl, tetrahydro-pyran-4-yl, 5-chloro-pyridin-2-yl, 1-carbamoyl-cyclobutyl, 5-fluoro-2-methyl-benzyl, 2-morpholin-4-yl-2-pyridin-3-yl-ethyl, 1-(3-methoxy-phenyl)-cyclobutyl, 5-methyl-pyridin-2-yl, 1-(tetrahydro-furan-2-yl)methyl, 1-dimethylaminomethyl-cyclopentyl, 2-(4-fluoro-phenyl)-1-methyl-ethyl, benzothiazol-2-yl, 1-(2-fluoro-phenyl)-cyclopropyl, 1-(2-methoxy-ethyl)-piperidin-4-yl, 2-hydroxy-1-pyridin-4-yl-ethyl, 1-(3,3,3-trifluoro-propyl)-azetidin-3-ylmethyl, 6-pyrrolidin-1-yl-pyridin-2-ylmethyl, 1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 2,3-dimethoxy-benzyl, 3-cyano-5-methyl-pyridin-2-yl, 2,3-dihydro-benzofuran-3-yl, 1-hydroxymethyl-cyclohexyl, 2,5-difluoro-benzyl, 4-dimethylamino-benzyl, 4-hydroxy-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 4-trifluoromethyl-pyridin-2-yl, 5-methyl-thiazol-2-yl, 6-trifluoromethyl-pyridin-3-yl, 5-hydroxy-1*H*-pyrazol-3-yl, 2-thiomorpholin-4-yl-ethyl, benzo[1,3]dioxol-5-ylmethyl, 2-amino-cyclohexyl, 3-dimethylamino-1-oxo-tetrahydro-1λ^4-thiophen-3-ylmethyl, 4-methyl-morpholin-2-ylmethyl, 1-(2-methoxy-phenyl)-cyclopropyl, 2-carboxy-1-(4-fluorophenyl)propan-2-yl, pyridin-2-ylmethyl, pyridazin-3-yl, 4-pyridin-2-yl-thiazol-2-yl, 1-(3,3,3-trifluoro-propyl)-piperidin-4-ylmethyl, 6-chloro-2-methyl-pyridin-3-yl, 6-hydroxy-pyridin-3-yl, 3-trifluoromethoxy-benzyl, 1-morpholin-4-yl-cyclopentylmethyl, 1-pyridin-2-yl-cyclobutylmethyl, indan-1-ylamide, 2-hydroxy-1-hydroxymethyl-1-methyl-ethyl, 5-hydroxymethyl-pyridin-2-yl, 5-fluoro-1-oxy-pyridin-2-yl, 6-methoxy-pyridin-2-yl, 1-methyl-1-pyridin-3-yl-ethyl, 6-methyl-pyridin-3-yl, 2-hydroxy-1-hydroxymethyl-propyl, 2-chloro-pyridin-3-yl, 3-methyl-3*H*-imidazol-4-ylmethyl, 6-fluoro-pyridin-2-yl, 3-dimethylamino-benzyl, 6-morpholin-4-yl-pyridin-3-yl, 1-*o*-tolyl-cyclopropyl, 1-(3,3,3-trifluoro-propyl)-piperidin-3-yl, 6-methanesulfonyl-4-methyl-pyridin-3-yl, 2-methyl-quinolin-4-yl, 1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-ylmethyl, benzooxazol-2-yl, 1-methyl-piperidin-4-ylmethyl, 2-(2,6-dimethyl-morpholin-4-yl)-2-methyl-propyl, 1-methyl-piperidin-2-ylmethyl, pyridin-4-ylmethyl, 4-hydroxymethyl-pyridin-2-yl, 5,7-dimethyl-pyrazolo[1,5-a]pyrimidin-2-yl, 6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl, 1-(5-methyl-pyridin-2-yl)-ethyl, 2-fluoro-pyridin-3-yl, morpholin-4-yl, 2-hydroxy-2-pyridin-4-yl-ethyl, pyridin-4-yl, 4-hydroxy-pyridin-2-yl, 3-methoxy-benzyl, 1-oxy-pyridin-2-yl, 1-ethyl-propyl, 6-carboxypyridin-2-yl, 1,2,2,6,6-pentamethyl-piperidin-4-yl, 6-methoxy-pyridin-3-yl, cyclopentyl, morpholin-2-ylmethyl, 1-(*tert*-butoxycarbonyl)azetidin-3-

yl)methyl, 2-dimethylamino-2-pyridin-3-yl-ethyl, 1-(4-methoxy-phenyl)-cyclobutyl, 3-hydroxy-benzyl, tetrahydro-furan-2-ylmethyl, 4-(*tert*-butoxycarbonyl)morpholin-2-ylmethyl, 1-(3-fluoro-phenyl)-cyclopropyl, 2-*o*-tolyl-ethyl, 3-hydroxymethyl-1-isobutyl-pyrrolidin-3-yl, 1-(2-methoxy-ethyl)-azetidin-3-yl, 6-morpholin-4-yl-pyridin-2-ylmethyl, 1,1-dioxo-tetrahydro-1λ^6-thiophen-3-ylmethyl, 2-(4-fluoro-phenoxy)-ethyl, 2,6-dimethyl-pyrimidin-4-yl, 1-hydroxymethyl-2-(3*H*-imidazol-4-yl)-ethyl, 4-methanesulfonyl-benzyl, 1-pyridin-3-yl-cyclopropyl, 9-methyl-9-aza-bicyclo[3.3.1]non-1-yl, 2,6-dimethyl-pyridin-3-yl, 4-hydroxy-benzyl, 2-oxo-2-phenyl-ethyl, 1-methyl-1*H*-pyrazol-3-ylmethyl, pyrimidin-2-yl, 5-methyl-pyrazin-2-yl, 1-(2-methoxy-pyridin-3-yl)-1-methyl-ethyl, 6-methanesulfonyl-2-methyl-pyridin-3-yl, 2-hydroxy-benzyl, 6-bromo-2-methyl-pyridin-3-yl, 2-methoxy-pyridin-3-yl, 1-(4-chloro-phenyl)-cyclobutyl, 2-(pyridine-2-sulfonyl)-ethyl, 1-pyridin-2-yl-cyclopropylmethyl, 1-methyl-1,2,3,4-tetrahydro-quinolin-7-yl, benzyl, 3,5-dimethyl-pyrazin-2-yl, 1-(2-hydroxy-pyridin-3-yl)-1-methyl-ethyl, 1-(ethoxycarbonyl)cyclobutyl, 1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylmethyl, quinolin-4-ylmethyl, 2-(4-fluoro-phenyl)-1-(2-hydroxy-ethylcarbamoyl)-1-methyl-ethyl, 2-morpholin-4-yl-pyridin-3-yl, 6-methyl-pyridin-2-yl, 3-difluoromethoxy-benzyl, 4-hydroxy-1-methyl-piperidin-4-ylmethyl, 1-(2,5-dimethylpyrrolidine-1-carbonyl)cyclopentyl, 2-methoxy-benzyl, 6-methyl-pyridin-2-ylmethyl, 3-chloro-pyridin-4-yl, 2-carboxypropan-2-yl, 6-chloro-pyridin-3-yl, 2-hydroxy-2-pyridin-3-yl-ethyl, 1-*p*-tolyl-cyclopropyl, 1-(3,3,3-trifluoro-propyl)-piperidin-4-yl, 4-methoxy-pyridin-2-yl, 3-azepan-1-yl-2,2-dimethyl-propyl, 1-(*tert*-butoxycarbonyl)azetidin-3-yl, 5-methyl-pyrazin-2-ylmethyl, 1-oxo-hexahydro-1λ^4-thiopyran-4-yl, 2-(2-chloro-phenyl)-ethyl, 3-chloro-5-trifluoromethyl-pyridin-2-ylmethyl, 2-hydroxy-1-hydroxymethyl-ethyl, (1-methyl-pyrrolidin-2-yl)-pyridin-2-yl, 5-fluoro-2-hydroxy-phenyl, methyl, 4-(methoxycarbonyl)-1-methylpiperidin-4-yl, 4-hydroxymethyl-1-methyl-piperidin-4-yl, 2-(2-hydroxymethyl-pyrrolidin-1-yl)-ethyl, 1-phenyl-cyclohexyl, 3-methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl, 1-cyano-cyclohexyl, 1-(5-methyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl, 2-cyanopropan-2-yl, 3-methyl-1-phenylureido, 1-carbamoyl-2,2-dimethyl-propyl, *tert*-butylamino, 2,2,2-trifluoro-1,1-dimethyl-ethyl, 2,2-dimethyl-1-methylcarbamoyl-propyl, 1-cyclopropyl-ethyl, amino, *N*-*tert*-butylmethylsulfonamido, 1,1-dimethyl-prop-2-ynyl, 2-methyl-1-(phosphonooxy)propan-2-yl, 1-*tert*-butyl-3-methylureido, 4-cyano-tetrahydro-pyran-4-yl, 1-methyl-cyclobutyl, 1-hydroxymethyl-2-methyl-propyl, cyclobutylamino, 1-cyano-cyclopentyl, cyano-dimethyl-methyl, 2,2-dimethyl-1-(methylcarbamoyl)-propyl, phenylamino, 1-hydroxymethyl-propyl, 1-methyl-1-(1*H*-tetrazol-5-yl)-ethyl, 3,3-dimethyl-1-(phosphonooxy)butan-2-yl, 2-hydroxy-1-tetrahydro-pyran-4-yl-ethyl, 1,2-dimethyl-propyl, 1-pyridin-2-yl-cyclobutyl, 1-hydroxymethyl-2-phenyl-ethyl, 4-methylcarbamoyl-tetrahydro-pyran-4-yl, 1-methyl-1-methylcarbamoyl-ethyl, 2,2-

dimethyl-1-morpholin-4-ylmethyl-propyl, 1-methylcarbamoyl-cyclopent-3-enyl, 2-methoxy-2-oxo-1-(pyridin-2-yl)ethyl, methylcarbamoyl-pyridin-2-yl-methyl, 1-methylcarbamoyl-cyclopentyl, 1-(*tert*-butylcarbamoyl)-2,2-dimethyl-propyl, 2,2-dimethyl-1-(pyridin-2-ylcarbamoyl)-propyl, 1-(pyridin-2-ylcarbamoyl)-cyclobutyl, 1-methylcarbamoyl-cyclobutyl, 2-(methylamino)-2-oxo-1-phenylethyl, pyrrolidin-1-yl, piperidin-1-yl, 2,6-dimethyl-piperidin-1-yl, 1-cyclopropylcarbamoyl-2,2-dimethyl-propyl, 2,2-dimethyl-1-(2,2,2-trifluoro-ethylcarbamoyl)-propyl, 1-ethylcarbamoyl-2,2-dimethyl-propyl, 2-hydroxy-1-(tetrahydro-pyran-4-yl)-ethyl, *N*-cyclobutylmethylsulfonamido, *N*-phenylmethylsulfonamido, 1-cyclopropyl-2-hydroxy-ethyl, 1,2,2-trimethyl-propyl, 2-oxo-1-(pyridin-2-yl)-2-(2,2,2-trifluoroethylamino)ethyl, 2,2-dimethyl-1-pyridin-2-yl-propyl, 1-methoxy-3,3-dimethyl-1-oxobutan-2-yl, 1-carboxy-2,2-dimethylpropyl, 1-(hydroxy-methyl-carbamoyl)-2,2-dimethyl-propyl, 1-dimethylcarbamoyl-2,2-dimethyl-propyl, 1-(azetidine-1-carbonyl)-2,2-dimethyl-propyl, 1-methoxycarbamoyl-2,2-dimethyl-propyl, 1-(methoxy-methyl-carbamoyl)-2,2-dimethyl-propyl, 1-*tert*-butoxycarbamoyl-2,2-dimethyl-propyl, 2,2-dimethyl-1-pyridin-2-yl-propyl, (1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)amino, 1-hydroxycarbamoyl-2,2-dimethyl-propyl, 1-hydroxymethyl-2-methyl-butyl, 1-(2-hydroxy-ethylcarbamoyl)-2,2-dimethyl-propyl, 1,1-*bis*-hydroxymethyl-propyl, 1-(5-fluoro-pyridin-2-yl)-2,2-dimethyl-propyl, 4-hydroxymethyl-tetrahydro-2*H*-pyran-4-yl, 1-(2-(*tert*-butoxycarbonylamino)-3-methylbutanoyloxy)-2-methylpropan-2-yl, 1-(2-amino-3-methylbutanoyloxy)-3-methylbutan-2-yl, 1-(2-amino-3-methylbutanoyloxy)-2-methylpropan-2-yl, 2-hydroxy-1-(tetrahydro-2*H*-pyran-4-yl)-ethyl, 1-(4-carboxybutanoyloxy)-2-methylpropan-2-yl, 1-(4-carboxybutanoyloxy)-3-methylbutan-2-yl, 1-(4-carboxybutanoyloxy)-3,3-dimethylbutan-2-yl, 1-(2-amino-3-methylbutanoyloxy)-3,3-dimethylbutan-2-yl, 2-(2-amino-3-methylbutanoyloxy)-1-(tetrahydro-2*H*-pyran-4-yl)ethyl, 3,3,3-trifluoro-1-hydroxymethyl-propyl, 3-fluoro-1-methoxy-3-methyl-1-oxobutan-2-yl, 1-ethoxy-4,4,4-trifluoro-1-oxo-3-(trifluoromethyl)butan-2-yl, 2-fluoro-1-hydroxymethyl-2-methyl-propyl, 1-(2-(tert-butoxycarbonylamino)-3-methylbutanoyloxy)-3,3-dimethylbutan-2-yl, 4,4,4-trifluoro-1-methoxy-1-oxobutan-2-yl, 2-fluoro-1,1-dimethyl-ethyl, 3-fluoro-2-(fluoromethyl)-1-methoxy-1-oxopropan-2-yl, 2-fluoro-1-fluoromethyl-1-hydroxymethyl-ethyl, 3-hydroxy-1-methoxy-2-methyl-1-oxopropan-2-yl, 2-carboxy-1-hydroxypropan-2-yl, 2,2,2-trifluoroethylamino, 1-fluoromethyl-2-methyl-propyl, 1-fluoromethyl-2,2-dimethyl-propyl, 3-methyl-oxetan-3-yl, 1-fluoromethyl-cyclobutyl, 1,1-*bis*-hydroxymethyl-2-methyl-propyl, 1-trifluoromethyl-cyclopropyl, 1-methyl-cyclopropyl, and 1-trifluoromethyl-cyclobutyl.

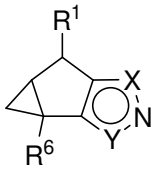
~~27.~~21. The compound according to any one of claims 1 to ~~26~~20, wherein R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl.

~~28.~~22. The compound according to any one of claims 1 to ~~26~~20, wherein R^9 is H.

~~29.~~23. The compound according to any one of claims 1 to ~~15~~9, wherein R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl each optionally substituted with one or more substituents selected from: carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

~~30.~~24. The compound according to any one of claims 1 to ~~15~~9, wherein R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: 4-cyclohexylmethyl-piperazin-1-yl, hexahydro-pyrrolo[1,2-a]pyrazin-2-yl, 5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl, 4-methoxy-2,3-dihydro-indol-1-yl, 2-phenyl-pyrrolidin-1-yl, 2-pyridin-2-yl-thiomorpholin-4-yl, 2-hydroxymethyl-2,3-dihydro-indol-1-yl, 4-hydroxy-piperidin-1-yl, hexahydro-pyrrolo[1,2-a]pyrazin-2-yl, 7-(methoxycarbonyl)-3,4-dihydro-1*H*-isoquinolin-2-yl, 7-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl, 1,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl, 5-fluoro-1,3-dihydro-isoindol-2-yl, 3-hydroxy-7,8-dihydro-5*H*-[1,6]naphthyridin-6-yl, 4-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperazin-1-yl, 1,3-dihydro-isoindol-2-yl, 3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazin-7-yl, 4-morpholin-4-yl-piperidin-1-yl, 3,4-dihydro-1*H*-isoquinolin-2-yl, 4-(3-methoxy-pyridin-2-yl)-piperazin-1-yl, 3-hydroxy-piperidin-1-yl, 4-(3-chloro-phenyl)-piperazin-1-yl, 6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl, morpholin-4-yl, 2-hydroxymethyl-pyrrolidin-1-yl, 1,3-dihydro-pyrrolo[3,4-c]pyridin-2-yl, 3-pyridin-4-yl-pyrrolidin-1-yl, 4-(pyridin-2-yloxy)-piperidin-1-yl, 3-pyridin-2-yl-pyrrolidin-1-yl, 7-methyl-3,4-dihydro-2*H*-[1,8]naphthyridin-1-yl, 3-pyridin-3-yl-pyrrolidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, 4-(4,6-dimethyl-pyrimidin-2-yl)-piperazin-1-yl, 2-methyl-3,4-dihydro-2*H*-quinolin-1-yl, 2-phenyl-morpholin-4-yl, and pyrazin-2-yl.

~~31.~~25. The compound according to claim 1, selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ic

wherein:

R^1 and R^6 are each independently selected from: H, and C_1-C_6 alkyl;

X is NR^7 and Y is $CC(O)N(R^8)R^9$; or

X is $CC(O)N(R^8)R^9$ and Y is NR^7;

R^7 ~~is $-R^{10}-R^{11}-R^{12}-R^{13}$; wherein:~~

~~R^{10} is selected from: C_1-C_6 alkylene, heteroarylene, and heterocyclylene; or R^{10} is absent;~~

~~R^{11} is selected from: $-C(O)NH-$ and C_1-C_6 alkylene; or R^{11} is absent;~~

~~R^{12} is C_1-C_6 alkylene; or R^{12} is absent; and~~

~~R^{13}~~ is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylsulfonyl, amino, C_3-C_7 cycloalkyl, cyano, C_2-C_8 dialkylamino, C_1-C_6 haloalkyl, halogen, and hydroxyl;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent;

R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

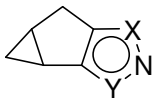
R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl,

heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, amino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

~~32.~~26. The compound according to claim 1, selected from compounds of Formula **Id** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Id

wherein:

X is NR^7 and Y is $CC(O)NHR^8$; or

X is $CC(O)NHR^8$ and Y is NR^7;

R^7 is selected from: aryl and heteroaryl; wherein said aryl and heteroaryl are each optionally substituted with one or two substituents selected from: cyano and halogen;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

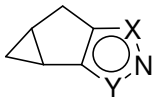
R^{14} is selected from: C_1-C_6 alkylene and C_3-C_7 cycloalkylene; wherein said C_1-C_6 alkylene is optionally substituted with one or more substituents selected from: C_1-C_6 alkyl, aryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl is optionally substituted with one substituent selected from: halogen, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH- and -C(O)O-; or R^{15} is absent;

R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkyl, C_1-C_6 alkylamino, amino, aryl, carboxy, cyano, C_1-C_6 haloalkyl, heteroaryl, hydroxyl, and phosphonooxy; wherein said aryl is optionally substituted with one hydroxyl group.

~~33.~~27. The compound according to claim 1, selected from compounds of Formula **Id** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Id

wherein:

X is NR^7 and Y is $CC(O)NHR^8$; or

X is $CC(O)NHR^8$ and Y is NR^7;

R^7 is selected from: aryl and heteroaryl; wherein said aryl and heteroaryl are each optionally substituted with one or two substituents selected from: fluoro, chloro, and cyano;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

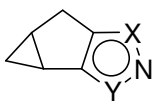
R^{14} is selected from: C_1-C_6 alkylene and C_3-C_7 cycloalkylene; wherein said C_1-C_6 alkylene is optionally substituted with one or more substituents selected from: tetrahydro-2*H*-pyranyl, hydroxyl, 2,2,2-trifluoroethyl, and fluoromethyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH- and -C(O)O-; or R^{15} is absent;

R^{16} is selected from: methylene, isopropyl-methylene, and propylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkyl, C_1-C_6 alkylamino, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, heteroaryl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said aryl and C_3-C_7 cycloalkyl are each optionally substituted with one or more substituents selected from: hydroxyl and trifluoromethyl.

~~34.~~28. The compound according to claim 1, selected from compounds of Formula **Id** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Id

wherein:

X is NR^7 and Y is $CC(O)NHR^8$; or

X is $CC(O)NHR^8$ and Y is NR^7;

R^7 is selected from: 2,4-difluoro-phenyl, 2,4-dichloro-phenyl, 5-chloro-pyridin-2-yl, 5-cyano-pyrazin-2-yl, pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 4-chloro-pyridin-2-yl, 4-fluoro-pyridin-2-yl, 4-cyano-pyridin-2-yl, and 4-oxy-pyrazin-2-yl;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

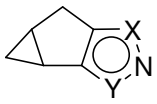
R^{14} is selected from: 1,1-cyclopropylene, 1,1-dimethyl-methylene, 1,1-cyclobutylene, *tert*-butyl-methylene, 1,1-dimethyl-ethylene, 1-*tert*-butyl-ethylene, 1-(tetrahydro-2*H*-pyran-4-yl)-ethylene, isopropyl-methylene, 1-hydroxymethyl-1-methyl-ethylene, phenyl-methylene, 1-isopropyl-ethylene, 1-(2,2,2-trifluoroethyl)-ethylene, and 1,1-di(fluoromethyl)-ethylene; or R^{14} is absent;

R^{15} is selected from: -C(O)NH- and -C(O)O-; or R^{15} is absent;

R^{16} is selected from: methylene, isopropyl-methylene, and propylene; or R^{16} is absent; and

R^{17} is selected from: is selected from: amino, 2-hydroxy-indan-1-yl, hydroxyl, carboxy, trifluoromethyl, methyl, *tert*-butyl, cyano, *tert*-butylamino, phosphonooxy, pyridin-2-yl, and fluoromethyl.

~~35.~~29. The compound according to claim 1, selected from compounds of Formula **Id** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Id

wherein:

X is NR^7 and Y is $CC(O)NHR^8$; or

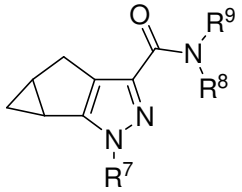
X is $CC(O)NHR^8$ and Y is NR^7;

R^7 is selected from: 2,4-difluoro-phenyl, 2,4-dichloro-phenyl, 5-chloro-pyridin-2-yl, 5-cyano-pyrazin-2-yl, pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 4-chloro-pyridin-2-yl, 4-fluoro-pyridin-2-yl, 4-cyano-pyridin-2-yl, and 4-oxy-pyrazin-2-yl; and

R^8 is selected from: 1-hydroxymethyl-2,2-dimethyl-propyl, 2-hydroxy-1,1-dimethyl-ethyl, 1-hydroxymethyl-cyclopropyl, 2-hydroxy-indan-1-yl, 1-hydroxymethyl-cyclobutyl, *tert*-butyl, 2-hydroxy-1-phenyl-ethyl, 2-hydroxy-1-hydroxymethyl-1-methyl-ethyl, *tert*-butylamino, 2,2,2-trifluoro-1,1-dimethyl-ethyl, 2-methyl-1-(phosphonooxy)propan-2-yl, 1-methyl-cyclobutyl,

1-hydroxymethyl-2-methyl-propyl, cyano-dimethyl-methyl, 2,2-dimethyl-1-(methylcarbamoyl)-propyl, 3,3-dimethyl-1-(phosphonooxy)butan-2-yl, 2-hydroxy-1-tetrahydro-pyran-4-yl-ethyl, 1,2-dimethyl-propyl, 1-pyridin-2-yl-cyclobutyl, 2-(methylamino)-2-oxo-1-phenylethyl, 2,2-dimethyl-1-pyridin-2-yl-propyl, 1-methoxy-3,3-dimethyl-1-oxobutan-2-yl, 1-(2-amino-3-methylbutanoyloxy)-3-methylbutan-2-yl, 1-(4-carboxybutanoyloxy)-3-methylbutan-2-yl, 3,3,3-trifluoro-1-hydroxymethyl-propyl, 2-fluoro-1,1-dimethyl-ethyl, 2-fluoro-1-fluoromethyl-1-hydroxymethyl-ethyl, 1-fluoromethyl-2,2-dimethyl-propyl, 1-fluoromethyl-cyclobutyl, 1-trifluoromethyl-cyclopropyl, and 1-trifluoromethyl-cyclobutyl.

~~36.~~30. The compound according to claim 1, selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ie

wherein:

R^7 is ~~$-R^{10}-R^{11}-R^{12}-R^{13}$; wherein:~~

~~R^{10} is selected from: C_1-C_6 alkylene, heteroarylene, and heterocyclylene; or R^{10} is absent;~~

~~R^{11} is selected from: $-C(O)NH-$ and C_1-C_6 alkylene; or R^{11} is absent;~~

~~R^{12} is C_1-C_6 alkylene; or R^{12} is absent; and~~

~~R^{13} is~~ selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylsulfonyl, amino, C_3-C_7 cycloalkyl, cyano, C_2-C_8 dialkylamino, C_1-C_6 haloalkyl, halogen, and hydroxyl;

R^8 is $-R^{14}-R^{15}-R^{16}-R^{17}$; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, carboxy, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl and aryl are optionally substituted with one substituent selected from: C_1-C_6 alkoxy, aryl, halogen, heteroaryl, and hydroxyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, -C(O)O-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with C_1-C_6 alkyl; or R^{15} is absent;

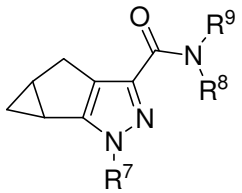
R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylsulfonyl, amino, aryl, carboxy, cyano, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heterocyclyl, and hydroxyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

~~37.~~31. The compound according to claim 1 or 2, selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof:



Ie

wherein:

R^7 ~~is R^{10}-R^{11}-R^{12}-R^{13}; wherein:~~

~~R^{10} is selected from: 1,1-dimethylethylene, 1,1-dimethylmethylene, ethylene, methylene, 1,4-piperidinylene, 2,5-pyrazinylene, and 2,4-pyridinylene; or R^{10} is absent;~~

~~R^{11} is selected from: -C(O)NH- and methylene; or R^{11} is absent;~~

~~R^{12} is methylene; or R^{12} is absent; and~~

~~R^{13}~~ is selected from: C_1-C_6 alkyl, aryl, C_3-C_7 cycloalkyl, heteroaryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl, aryl, and heteroaryl are each optionally substituted with one or two substituents selected from: fluoro, bromo, chloro, methoxy, cyano, methyl, *tert*-butyl, isopropyl, hydroxyl, ethyl, heptafluoropropyl, cyclobutyl, trifluoromethyl, cyclopropyl, dimethylamino, methoxy, ethoxy, methylamino, propyl, amino, and methanesulfonyl;

R^8 is -R^{14}-R^{15}-R^{16}-R^{17}; wherein:

R^{14} is selected from: C_1-C_6 alkylene, C_3-C_7 cycloalkenylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said C_1-C_6 alkylene and heterocyclylene are each optionally substituted with one or more substituents selected from: methyl, *tert*-butyl, ethyl, tetrahydro-2*H*-pyranyl, isopropyl, benzyl, pyridinyl, hydroxymethyl, 4-fluoro-phenyl, *tert*-butoxycarbonyl, carboxy, methoxymethyl, hydroxyethyl, tetrahydro-furanyl, 3*H*-imidazolylmethyl, hydroxyl, pyrrolidinyl, and cyclopropyl; or R^{14} is absent;

R^{15} is selected from: -C(O)NH-, -C(O)-, C_1-C_6 alkylene, C_3-C_7 cycloalkylene, heteroarylene, and heterocyclylene; wherein said heterocyclylene is optionally substituted with methyl; or R^{15} is absent;

R^{16} is selected from: ethylene and methylene; or R^{16} is absent; and

R^{17} is selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylcarboxamide, C_2-C_6 alkynyl, ureyl, amino, aryl, arylamino, arylcarbonyl, aryloxy, carbo-C_1-C_6-alkoxy, carboxamide, carboxy, cyano, C_3-C_7 cycloalkyl, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkylamino, C_2-C_8 dialkylamino, C_2-C_8 dialkylsulfonamide, C_1-C_6 haloalkyl, heteroaryl, heteroaryloxy, heterobicyclyl, heterocyclyl, hydroxyl, and phosphonooxy; wherein said C_1-C_6 alkylamino, aryl, arylamino, aryloxy, C_5-C_{11} bicycloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylamino, heteroaryl, heterobicyclyl, heterocyclyl, and ureyl are each optionally substituted with one or more substituents selected from: amino, 1-*tert*-butoxycarbonylamino, methyl, 1-*tert*-butoxycarbonyl, ethyl, hydroxyl, isopropyl, *tert*-butyl, fluoro, chloro, methoxy, methanesulfonyl, carboxy, trifluoromethoxy, difluoromethoxy, dimethylamino, methoxycarbonyl, ethoxycarbonyl, carboxy, carboxamide, trifluoromethyl, diethylamino, cyano, *tert*-butylamino, cyclopropyl, cyclobutyl, phenyl, bromo, and 1-methyl-pyrrolidinyl; and

R^9 is selected from H, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl; or

R^8 and R^9 together with the nitrogen atom to which they are both bonded form a group selected from: heterocyclyl and heterobicyclyl, each optionally substituted with one or more substituents selected from: carbo-C_1-C_6-alkoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, aryl, carbo-C_1-C_6-alkoxy, C_1-C_6 haloalkyl, halogen, heteroaryl, heteroaryloxy, heterocyclyl, and hydroxyl; wherein

said aryl, C_1-C_6 alkyl, and heteroaryl are optionally substituted with one substituent selected from: C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, and hydroxyl.

~~38.~~32. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

(1a*R*,5a*R*)-2-(5-Chloro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 151);

(1a*R*,5a*R*)-2-(2,4-Dichloro-phenyl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-hydroxymethyl-cyclopropyl)-amide (Compound 174);

(1a*R*,5a*R*)-2-(5-Cyano-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 264);

(1a*R*,5a*R*)-2-(5-Fluoro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 309);

(1a*R*,5a*R*)-2-(2,4-Difluoro-phenyl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 493);

1-(2,4-Difluoro-phenyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 515);

(1a*R*,5a*R*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid tert-butylamide (Compound 593);

(1a*R*,5a*R*)-2-(4-Chloro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (cyano-dimethyl-methyl)-amide (Compound 625);

(1a*R*,5a*R*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 642);

(1a*R*,5a*R*)-2-(4-Cyano-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 644);

Phosphoric acid mono-(2-{[(1a*R*,5a*R*)-2-(4-cyano-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl]-amino}-2-methyl-propyl) ester (Compound 646);

(1a*R*,5a*R*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid [2,2-dimethyl-1-((*S*)-methylcarbamoyl)-propyl]-amide (Compound 667);

Phosphoric acid mono-{(*S*)-3,3-dimethyl-2-[((1a*R*,5a*R*)-2-pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl)-amino]-butyl} ester (Compound 683);

(1a*R*,5a*R*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-2-hydroxy-1-tetrahydro-pyran-4-yl-ethyl)-amide (Compound 684);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl)-amide (Compound 690);

(1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 696);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-hydroxymethyl-cyclobutyl)-amide (Compound 698);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 699);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-pyridin-2-yl-cyclobutyl)-amide (Compound 700);

Phosphoric acid mono-((*S*)-3,3-dimethyl-2-{[(1a*R*,5a*R*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl]-amino}-butyl) ester (Compound 703);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-2,2-dimethyl-1-methylcarbamoyl-propyl)-amide (Compound 704);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-methylcarbamoyl-phenyl-methyl)-amide (Compound 722);

(*S*)-3,3-Dimethyl-2-{[(1a*R*,5a*R*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl]-amino}-butyric acid methyl ester (Compound 746);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclopropyl)-amide (Compound 764);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclobutyl)-amide (Compound 765);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*R*)-2,2-dimethyl-1-pyridin-2-yl-propyl)-amide (Compound 766);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-2,2-dimethyl-1-pyridin-2-yl-propyl)-amide (Compound 767);

(1a*R*,5a*R*)-2-(4-Cyano-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-amide (Compound 820);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-methyl-cyclobutyl)-amide (Compound 821);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*R*)-1,2-dimethyl-propyl)-amide (Compound 828);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid [(*S*)-2-hydroxy-1-(tetrahydro-pyran-4-yl)-ethyl]-amide (Compound 841);

(1a*R*,5a*R*)-Pentanedioic acid mono-((*S*)-3-methyl-2-{[(1a*R*,5a*R*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl]-amino}-butyl) ester (Compound 844);

(1a*S*,5a*S*)-(*S*)-2-Amino-3-methyl-butyric acid (*S*)-3,3-dimethyl-2-{[2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carbonyl]-amino}-butyl ester (Compound 848);

(1a*S*,5a*S*)-2-(4-Chloro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-fluoro-1-fluoromethyl-1-hydroxymethyl-ethyl)-amide (Compound 889);

(1a*S*,5a*S*)-2-(4-Cyano-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-3,3,3-trifluoro-1-hydroxymethyl-propyl)-amide (Compound 891);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl)-amide (Compound 896);

(1a*S*,5a*S*)-2-(4-Chloro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-fluoro-1,1-dimethyl-ethyl)-amide (Compound 897);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid *N*'-tert-butyl-hydrazide (Compound 902);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-fluoro-1,1-dimethyl-ethyl)-amide (Compound 904);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*R*)-1,2-dimethyl-propyl)-amide (Compound 912);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-2-hydroxy-1-phenyl-ethyl)-amide (Compound 913);

(1a*R*,5a*R*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-fluoromethyl-2,2-dimethyl-propyl)-amide (Compound 918);

~~(1a*S*,5a*S*) 2 (4 Oxy pyrazin 2 yl) 1a,2,5,5a tetrahydro 1*H* 2,3 diaza-cyclopropa[a]pentalene 4 carboxylic acid (2,2,2 trifluoro 1,1 dimethyl ethyl) amide;~~

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((1*S*,2*S*)-2-hydroxy-indan-1-yl)-amide (Compound 920);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((1*S*,2*R*)-2-hydroxy-indan-1-yl)-amide (Compound 921);

(1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-fluoromethyl-cyclobutyl)-amide (Compound 924);

(1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclobutyl)-amide (Compound 926);

(1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2,2,2-trifluoro-1,1-dimethyl-ethyl)-amide (Compound 927);

(1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclopropyl)-amide (Compound 930); and

(1a*R*,5a*R*)-2-(4-Fluoro-pyridin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (Compound 931).

33. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 696); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

34. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 699); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

35. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclopropyl)-amide (Compound 764); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

36. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclobutyl)-amide (Compound 765); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

37. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-(4-Oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((1*S*,2*R*)-2-hydroxy-indan-1-yl)-amide (Compound 921); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

38. The compound according to claim 1, selected from: (1a*S*,5a*S*)-2-Pyrazin-2-yl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1-trifluoromethyl-cyclobutyl)-amide (Compound 926); and pharmaceutically acceptable salts, solvates, hydrates, and *N*-oxides thereof.

39. A pharmaceutical composition comprising a compound according to any one of claims 1 to 38 and a pharmaceutically acceptable carrier.

40. A process for preparing a pharmaceutical composition comprising admixing a compound according to any one of claims 1 to 38 and a pharmaceutically acceptable carrier.

~~40. A method for the treatment of a cannabinoid receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 38 or a pharmaceutical composition according to claim 39.~~

~~41. A method for the treatment of a CB_2 receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 38 or a pharmaceutical composition according to claim 39.~~

~~42. A method for the treatment of a CB_1/CB_2 receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 38 or a pharmaceutical composition according to claim 39.~~

~~43. A method for the treatment of pain in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 38 or a pharmaceutical composition according to claim 39.~~

~~44. A method for the treatment of osteoarthritis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 38 or a pharmaceutical composition according to claim 39.~~

41. Use of a compound according to any one of claims 1 to 38, in the manufacture of a medicament for modulating the activity of a cannabinoid CB_2 receptor.

~~45.~~42. Use of a compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, in the manufacture of a medicament for the treatment of a cannabinoid receptor-mediated disorder.

~~46.~~43. ~~Use of a compound according to any one of claims 1 to 38, in the manufacture of a medicament for the treatment of a~~The use of claim 42, wherein the cannabinoid receptor-mediated disorder is a CB_2 receptor-mediated disorder.

~~47.~~44. ~~Use of a compound according to any one of claims 1 to 38, in the manufacture of a medicament for the treatment of a~~The use of claim 42, wherein the cannabinoid receptor-mediated disorder is a CB_1/CB_2 receptor-mediated disorder.

~~48.~~45. Use of a compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, in the manufacture of a medicament for the treatment of pain.

~~49.~~46. Use of a compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, in the manufacture of a medicament for the treatment of osteoarthritis.

~~50. A compound according to any one of claims 1 to 38, for use in a method of treatment of the human or animal body by therapy.~~

47. A compound according to any one of claims 1 to 38, for use in modulating the activity of a cannabinoid CB_2 receptor.

~~51.~~48. A compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, for use in ~~a method of~~the treatment of a cannabinoid receptor-mediated disorder.

~~52.~~49. ~~A compound according to any one of claims 1 to 38, for use in a method of treatment of a CB_2 receptor-mediated disorder~~The compound or pharmaceutical composition for use according to claim 48, wherein the cannabinoid receptor-mediated disorder is a CB_2 receptor-mediated disorder.

~~53.~~50. The compound or pharmaceutical composition for use according to claim 48, wherein the cannabinoid receptor-mediated disorder is ~~A compound according to any one of claims 1 to 38, for use in a method of treatment of~~ a CB_1/CB_2 receptor-mediated disorder.

~~54.~~51. A compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, for use in ~~a method of~~the treatment of pain.

~~55.~~52. A compound according to any one of claims 1 to 38, or a pharmaceutical composition according to claim 39, for use in ~~a method of~~the treatment of osteoarthritis.

~~56. A process for preparing a pharmaceutical composition comprising admixing a compound according to any one of claims 1 to 38 and a pharmaceutically acceptable carrier.~~