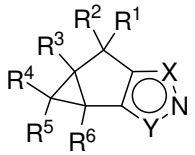
cancerous cell lines (Munro, S. *et al.* (1993) *Nature* 365:61-65; and as reviewed in Pacher, P. *et al.* (2006) *Pharmacol. Rev*. 58(3): 389-462). As such, CB_1 is believed to be primarily responsible for mediating the psychotropic effects of cannabinoids on the body, whereas CB_2 is believed to be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

One example of the present 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;

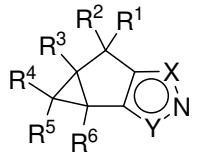
R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

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



Ia

wherein:

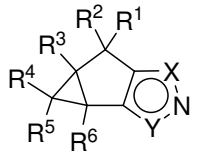
R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from: H and C_1-C_6 alkyl;

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 example of the present disclosure relates to processes for preparing pharmaceutical compositions comprising admixing a compound of the present 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 example of the present disclosure relates to pharmaceutical compositions comprising a compound of the present 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 example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

One example of the present 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 disclosure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

These and other examples of the 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**.

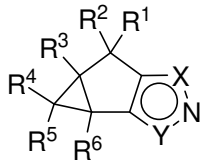
Figure 3 shows the effect of 10 mg/kg of Compound **493** on paclitaxel-induced allodynia in rats. See Example **8**.

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 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^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.

8. The compound according to any one of claims 1 to 6, wherein 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.

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.

10. The compound according to any one of claims 1 to 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.

11. The compound according to any one of claims 1 to 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.

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

13. The compound according to any one of claims 1 to 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.

14. The compound according to any one of claims 1 to 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.

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

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

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

18. The compound according to any one of claims 1 to 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.

19. The compound according to any one of claims 1 to 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.

20. The compound according to any one of claims 1 to 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.

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

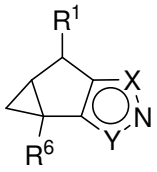
22. The compound according to any one of claims 1 to 20, wherein R^9 is H.

23. The compound according to any one of claims 1 to 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.

24. The compound according to any one of claims 1 to 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.

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 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;

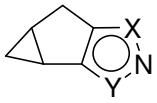
R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

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.

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:

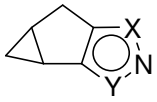
R^{14} is selected from: C_1-C_6 alkylene and C_3-C_7 cycloalkylene; wherein said C_1-C_6 alkylene is optionally substituted with one or more substituents selected from: C_1-C_6 alkyl, aryl, heterocyclyl, and hydroxyl; wherein said C_1-C_6 alkyl is optionally substituted with one substituent selected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

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:

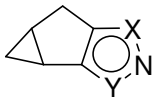
R^{14} is selected from: C_1-C_6 alkylene and C_3-C_7 cycloalkylene; wherein said C_1-C_6 alkylene is optionally substituted with one or more substituents selected from: tetrahydro-2*H*-pyranyl, hydroxyl, 2,2,2-trifluoroethyl, and fluoromethyl; or R^{14} is absent;

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.

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:

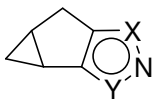
R^{14} is selected from: 1,1-cyclopropylene, 1,1-dimethyl-methylene, 1,1-cyclobutylene, *tert*-butyl-methylene, 1,1-dimethyl-ethylene, 1-*tert*-butyl-ethylene, 1-(tetrahydro-2*H*-pyran-4-yl)-ethylene, isopropyl-methylene, 1-hydroxymethyl-1-methyl-ethylene, phenyl-methylene, 1-isopropyl-ethylene, 1-(2,2,2-trifluoroethyl)-ethylene,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

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:

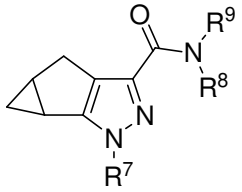
X is NR^7 and Y is $CC(O)NHR^8$; or

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.

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 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;

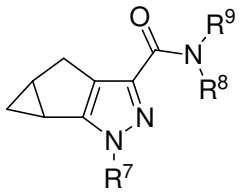
R^{16} is C_1-C_6 alkylene; or R^{16} is absent; and

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.

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 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.

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 ((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.

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.

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.

43. The use of claim 42, wherein the cannabinoid receptor-mediated disorder is a CB_2 receptor-mediated disorder.

44. The use of claim 42, wherein the cannabinoid receptor-mediated disorder is a CB_1/CB_2 receptor-mediated disorder.

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.

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.

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

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

49. The compound or pharmaceutical composition for use according to claim 48, wherein the cannabinoid receptor-mediated disorder is a CB_2 receptor-mediated disorder.

50. The compound or pharmaceutical composition for use according to claim 48, wherein the cannabinoid receptor-mediated disorder is a CB_1/CB_2 receptor-mediated disorder.

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

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