JP2023522436A インターロイキン阻害剤

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FIELD OF THE INVENTION The present invention relates to diazine and triazine compounds having activity as interleukin inhibitors, particularly interleukin-1beta, 2, 4, 6, 8, 13 and 17, and related disorders, particularly Alzheimer's disease, Parkinson's disease. , relates to compounds for use in the treatment of asthma, rejection of solid organ transplants.

BACKGROUND OF THE INVENTION WO2009090431A discloses triazines of the formula where the A ring can be an optionally substituted sulphur-containing heterocycle such as thienyl and benzothienyl.

WO2009090431A further discloses triazines of the formula:

The compounds of WO2009090431A are said to have activity as voltage-gated sodium channel blockers.

The literature (Foreman et al., Pharmacology, Biochemistry and Behavior 89 (2008), 523-534) describes studies of the compound JZP-4, which is an animal model of anticonvulsant, antimanic, and antidepressant effects. It is said to be a calcium and sodium channel blocker in The structure of ZP-4 is as follows.

GB735702B describes 2,4-diaminopyrimidines and methods for their preparation. The compound is said to be effective in treating malarial infections. Inhibition of interleukins is known to be useful in many diseases and conditions. Inhibition of interleukin-1 beta has been reported in epilepsy, especially drug-refractory epilepsy, among others (Vezzani et al., 2019, Nature Reviews Neurology, vol. 15, no. 8, pp. 459-472 and Kumar et al., 2019, JCI Insight, vol. 4). No. 8), systemic juvenile arthritis (https://juvenilearthritisnews.com/arcalyst-rilonacept/), oncology, especially breast cancer (more specifically metastatic breast cancer), colon cancer, lung cancer, head and neck cancer and melanoma (Tulotta and Otterwell, Endocrine-Related Cancer 2018, 25(7), R421-R434; and Baker et al., Frontiers in Immunology, 2019, 10). IL-1 beta is associated with glaucoma, stroke, brain injury, diabetic retinopathy, Alzheimer's disease, and multiple sclerosis (Mendiola, A. and Cardona, A., 2017, Journal of Neural Transmission, vol. 125, no. 5; 781-795), acute brain injury (Brough et al., 2011, Trends in Pharmacological Sciences, 32:10, 617-622), spinal cord injury (Boato et al., 2013, Journal of Neuroinflammation, 10:1). , motor neuron diseases (Meissner et al., 2010, Proceedings of the National Academy of Sciences, vol. 107, no. 29, pp. 13046-13050), Parkinson's disease (Erekat and Al-Jarrah, 2018, Medical Science Monitor, 24 Volume, 7524 7531), neuropathic pain (Hung et al., 2017, Scandinavian Journal of Pain, 17:1, 287-293), migraine (He et al., 2019, Journal of Neuroinflammation, 16:1). , anxiety (McKim et al., 2017, Molecular Psychiatry, 23:6, 1421-1431), trigeminal autonomic cranialgia (Neeb et al., 2016, The Journal of Headache and Pain, 17:1), It is also useful in the treatment of inflammatory pain (Dinarello et al., 2012, Nature Reviews Drug Discovery, 11:8:633-652).

Interleukin-2 inhibitors are known to have activity as immunosuppressive and anti-inflammatory agents and are useful for reducing organ transplant rejection (Karahan et al., 2019, Transplantation Proceedings, 51 Vol. 4, pp. 1074-1077). An IL-2 inhibitor has been approved by the FDA for the treatment of relapsing multiple sclerosis (Pharmacy Today, August 2016, 22:8, 38).

Interleukin-6 inhibitors are indicated for the treatment of uveitis (Karkhur et al., J Ophthal Inflamm Infect 9:17, 2019), rheumatoid arthritis (Navarro et al., Seminars in arthritis and rheumatism, 2014, 43:4). No.: 458-469), and in the treatment of systemic juvenile idiopathic arthritis (Yokota et al., Arthritis and rheumatism, 2005, 52, No. 3: 818-825).

Interleukins 4 and 13 are important drivers of type 2 inflammation, thus IL-4 and IL-13 inhibitors are useful in atopic dermatitis, asthma, chronic sinusitis with nasal polyposis, eosinophilic esophagus Useful potential treatments for diseases and conditions caused by allergy and other type 2 inflammation, including inflammation, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, alopecia areata, pulmonary tuberculosis, Hodgkin's disease, and food and environmental allergies. Law. In particular, IL-4 has been used in the treatment of chronic asthma (Steinke and Borish, Respir Res. 2001; 2:2:66-70), atopic dermatitis, chronic rhinosinusitis, sleep apnea and eczema. It is useful in therapy (Junttila, Frontiers in Immunology, 2018, 9:888). IL-13 is also useful in the treatment of Hodgkin's disease (Junttila, Frontiers in Immunology, 2018, 9:888).

Interleukin 17 inhibitors are indicated for the treatment of multiple sclerosis (Kolbinger et al., 2016, Current Drug Targets (2016) 17:1882), ischemic stroke (Gelderblom et al., 2012, Blood 120:18). 3793-3802) and in the treatment of neuropathic pain (Hung et al., A., 2017, Scandinavian Journal of Pain, 17:1, 287-293).

Overview The present invention relates to asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer. , non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis A compound of formula (I), or a salt, tautomer or solvate thereof, for use in treating a disorder or condition

(wherein X is N and Y is C, or X is C and Y is N, or X and Y are both N and A is 1, 2 or 3 a substituted 3- to 10-membered heterocycle containing a sulfur atom, wherein the heterocycle is C1-6 optionally substituted with one or more of (i) halogen, (ii) all halogen, hydroxy, and aryl from alkyl, C2-6 alkenyl, C2-6 alkynyl, or C1-6 alkoxy, and (iii) amino, mono- or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups have two or more selected substituents, or A is a group

wherein · represents a point of attachment, and R1 is hydrogen or from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl selected substituents, any of which are optionally substituted with hydroxy, halogen, carboxamido, haloC1-6 alkyl, C1-6 alkyl or C1-6 alkoxy, or Y is N, and unsubstituted, R2 is amino, C1-10 alkyl or phenyl and R3 is phenyl, xantyl or naphthyl, each optionally with 1 to 5 substituents selected from halogen or C1-C6 alkoxy groups; substituted, wherein R4 is selected from hydrogen, C1-C6 alkyl, C3-C8 cycloalkyl, phenyl, xanthyl or naphthyl, wherein phenyl or naphthyl is 1 to 5 selected from halogen or C1-C6 alkoxy groups preferably 2 to 5 substituents, R5 is hydrogen, N* is =NH if R1 is hydrogen or a substituent, or N * is a NRaRb group, where Ra and Rb are independently H or an alkyl group, or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups)I will provide a.

The present invention further provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer. , non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis A method of treating a disorder or condition comprising: administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a salt, tautomer or solvate thereof Provide a method that includes

The invention further provides for epilepsy, multiple sclerosis, glaucoma and uveitis, brain trauma and brain ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative disease, motor neuron disease, Alzheimer's disease, Parkinson's disease. chronic inflammatory pain, neuropathic pain, migraine,

bipolar disorder, mood, anxiety, cognitive disorders, schizophrenia, and trigeminal autonomic cranialgia or a salt, tautomer or solvate thereof of formula (IA) for

(wherein X is N and Y is C, or X is C and Y is N and A is a substituted 3- to 10-membered is a heterocycle, said heterocycle being (i) halogen, (ii) C1-6 alkyl, C2-6 alkenyl, C2-6, all optionally substituted with one or more of halogen, hydroxy, and aryl; alkynyl, or C1-6 alkoxy, and (iii) two or more substituents selected from amino, mono- or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups; and R1 is hydrogen or a substituent selected from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl, which are any is optionally substituted with hydroxy, halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted, R2 is amino, C1- 10 alkyl or phenyl and N* is =NH if R is hydrogen or a substituent, or N* is a NRaRb group and Ra and Rb are independently H or an alkyl group or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups).

The invention further provides for epilepsy, multiple sclerosis, glaucoma and uveitis, brain trauma and brain ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative disease, motor neuron disease, Alzheimer's disease, Parkinson's disease. chronic inflammatory pain, neuropathic pain, migraine, bipolar disorder, mood, anxiety, cognitive disorders, schizophrenia, and trigeminal autonomic cerebral pain. administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (IA) or a salt, tautomer or solvate thereof.

The present invention further provides compounds of formula (IA), or salts, tautomers or solvates thereof

(wherein X is N and Y is C, or X is C and Y is N and A is a substituted 3- to 10-membered is a heterocycle, wherein the heterocycle is (i) halogen, (ii) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, all optionally substituted with one or more of halogen, hydroxy, and aryl; or C1-6 alkoxy, and (iii) two or more substituents selected from amino, monosubstituted or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups; , R1 is hydrogen or a substituent selected from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl, any of which are hydroxy , halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted, R2 is amino , C1-10 alkyl or phenyl, and N* is =NH if R1 is hydrogen or a substituent, or N* is an NRaRb group, and Ra and Rb are independently H or an alkyl group or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups with the proviso that X is C, Y is N and A is halogen is optionally substituted thienyl, R2 is not C1-C3 alkyl).

The present invention further provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer. , non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell is selected from metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis A compound of formula (IB), or a salt, tautomer or solvate thereof, for use in treating a disorder or condition

(wherein R3 is phenyl, xantyl or naphthyl, each optionally substituted with 1 to 5 substituents selected from halogen or C1-C6 alkoxy groups, R4 is hydrogen, C1-C6 selected from alkyl, C3-C8 cycloalkyl, phenyl, xantyl or naphthyl, phenyl or naphthyl optionally with 1 to 5, preferably 2 to 5 substituents selected from halogen or C1-C6 alkoxy groups optionally substituted; R5 is hydrogen and R1 is selected from hydrogen or C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl any of which are optionally substituted with hydroxy, halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted and R2 is amino, C1-10 alkyl or phenyl, N* is amino if R1 is hydrogen, =NH if R1 is a

substituent, or N* is NRaRb and Ra and Rb are independently H or an alkyl group, or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups). .

The present invention further provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer. , non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis A method of treating a disorder or condition comprising: administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (IB) or a salt, tautomer or solvate thereof Provide a method that includes

Figure 2 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL) 1 beta. FIG. 4 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL)6. FIG. 2 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL)8. FIG. 2 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL) 17A. FIG. 4 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine on interleukin (IL) 17A. FIG. 3 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4- on interleukin (IL)-8. FIG. 2 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4- on interleukin (IL)-6.

Detailed Description It will be appreciated that formulas (IA) and (IB) are subformulas of formula (I).

The compounds of formulas (I), (IA) and (IB) are inhibitors of interleukin-1 beta, 2, 4, 6, 8, 13 or 17 and are therefore useful in the treatment of many disorders and conditions. .

As Embodiment 1, the present invention provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer, non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and A compound of formula (I), or a salt, tautomer or solvate thereof, for use in treating a disorder or condition selected from pulmonary tuberculosis

(wherein X is N and Y is C, or X is C and Y is N, or X and Y are both N and A is 1, 2 or 3 a substituted 3- to 10-membered heterocycle containing a sulfur atom, wherein the heterocycle is C1-6 optionally substituted with one or more of (i) halogen, (ii) all halogen, hydroxy, and aryl from alkyl, C2-6 alkenyl, C2-6 alkynyl, or C1-6 alkoxy, and (iii) amino, mono- or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups have two or more selected substituents, or A is a group

wherein · represents a point of attachment, and R1 is hydrogen or from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl selected substituents, any of which are optionally substituted with hydroxy, halogen, carboxamido, haloC1-6 alkyl, C1-6 alkyl, or C1-6 alkoxy, or Y is N; and unsubstituted, R2 is amino, C1-10 alkyl or phenyl and R3 is phenyl, xantyl or naphthyl, each with 1 to 5 substituents selected from halogen or C1-C6 alkoxy groups, preferably is optionally substituted with 2-5 substituents; R4 is selected from hydrogen, C1-C6 alkyl, C3-C8 cycloalkyl, phenyl, xanthyl or naphthyl, wherein phenyl or naphthyl is halogen or C1- optionally substituted with 2 to 5 substituents selected from C6 alkoxy groups, R5 is hydrogen and N* is =NH if R1 is hydrogen or a substituent, or N* is a NRaRb group, where Ra and Rb are independently H or an alkyl group, or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups provided).

Compounds for use as defined in embodiment 1 are preferably selected from: 3,5-diamino-6-(2-thienyl)-1,2,4-triazine; 5-diamino-6-(3-thienyl)-1,2,4-triazine; 3,5-diamino-6-[3-(2,5dichlorothienyl)]-1,2,4-triazine; 5-diamino-6-[2-(3,4,5trichlorothienyl)]-1,2,4-triazine; 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino-2-

methyl-1,2,4-triazine; 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3 (5)-imino-2-ethyl-1,2,4-triazine; 5(3)-amino-6-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro -3(5)-imino-2-methyl-1,2,4-triazine; 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2, 5)-dihydro-3(5)-imino-2-methyl-1,2,4-triazine; 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2, 3(2,5)-dihydro-3(5)-imino-2-ethyl-1,2,4-triazine; 3,5-diamino-6-[2-(4,5-dibromothienyl)]-1,2,4-triazine;3,5-diamino-6-[2-(5-bromothienyl)]-1,2,4-triazine;3,5-diamino-6-[2-(3-bromothienyl)]-1,2,4-triazine; 3,5-diamino-6-[2-(5-chlorothienyl)]-1,2,4-triazine; 3,5-diamino-6-[2-(benzo[b]thienyl)]-1,2,4-triazine; 3,5-diamino-6-[2-(3-chlorobenzo[b]thienyl)]-1,2,4-triazine. 2,6-diamino-3-(2-thienyl)-pyrazine (also known as 3,5-diamino-6-(2-thienyl)-pyrazine), 2,4-diamino-5-(2-thienyl))-pyrimidine (also called 3,5-diamino-6-(2-thienyl)-pyrimidine), 2,6-diamino-3-(3-thienyl)-pyrazine (also called 3,5-diamino -6-(3-thienyl)-pyrazine), 2,4-diamino-5-(3-thienyl)-pyrimidine (also called 3,5-diamino-6-(3-thienyl)-pyrimidine)), 2,6-diamino-3-[3-(2,5-dichlorothienyl)]-pyrazine (also known as 3,5-diamino-6-[3-(2,5-dichlorothienyl)]-pyrazine 2,4-diamino-5-[3-(2,5-dichlorothienyl)]-pyrimidine (also known as 3,5-diamino-6-[3-(2,5-dichlorothienyl)] -pyrimidine), 2,6-diamino-3-[2-(3,4,5-trichlorothienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(3,4, 5-trichlorothienyl)]-pyrazine), 2,4-diamino-5-[2-(3,4,5 trichlorothienyl)]-pyrimidine (also called 3,5-diamino-6-[2- (3,4,5 trichlorothienyl)]-pyrimidine), 2(6)-amino-3-(2-thienyl)-2,3(2,5)-dihydro-6(2)-imino-5 -methyl-pyrazine (also known as 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrazine), 4(2)-amino-5-(2-thienyl)-2,3(2,5)-dihydro-2(4)-imino-1-methyl-pyrimidine (also known as 5(3)-amino-6 -(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrimidine), 2(6)-amino-3-(2-thienyl)-2 , 3(2,5)-dihydro-6(2)-imino-5-ethyl-pyrazine (also known as 5(3)-amino-6-(2-thienyl)-2,3(2,5)- dihydro-3(5)-imino-2-ethyl-pyrazine), 4(2)-amino-5-(2-thienyl)-2,3(2,5)-dihydro-2(4)-imino -1-ethyl-pyrimidine (also known as 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino-2-ethyl-pyrimidine)), 2(6)-amino-3-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro-6(2)-imino-5-methyl-pyrazine (also known as , 5(3)-amino-6-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrazine)) , 4(2)-amino-5-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro-2(4)-imino-1-methyl-pyrimidine (also known as 5(3)-amino-6-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrimidine), 2 (6)-amino-3-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-6(2)-imino-5-methyl-pyrazine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrazine) , 4(2)-amino-5-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-2(4)-imino-1-methyl-pyrimidine (alias As, 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrimidine 2(6)-amino-3-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-6(2)-imino-5-ethyl-pyrazine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-3(5)-imino-2-ethyl- pyrazine), 4(2)-amino-5-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-2(4)-imino-1-ethyl -pyrimidine (aka 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-3(5)-imino-2-2,6-diamino-3-[2-(4,5-dibromothienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(4,5-dibromo thienyl)]-pyrazine), 2,4-diamino-5-[2-(4,5-dibromothienyl)]-pyrimidine (also known as 3,5-diamino-6-[2-(4,5 -dibromothienyl)]-pyrimidine), 2,6-diamino-3-[2-(5-bromothienyl)]-pyrazine (also called 3,5-diamino-6-[2-(5-bromo thienyl)]-pyrazine), 2,4-diamino-5-[2-(5-bromothienyl)]-pyrimidine (also known as 3,5-diamino-6-[2-(5-bromothienyl)]-pyrimidine), 2,6-diamino-3-[2-(3-bromothienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(3-bromothienyl)]- 2,4-diamino-5-[2-(3-bromothienyl)]-pyrimidine (also known as 3,5-diamino-6-[2-(3-bromothienyl)]-pyrimidine) 2,6-diamino-3-[2-(5-chlorothienyl)]-pyrazine (also called 3,5-diamino-6-[2-(5-chlorothienyl)]-pyrazine) , 2,4-diamino-5-[2-(5-chlorothienyl)]-pyrimidine (also called 3,5-diamino-6-[2-(5-chlorothienyl)]-pyrimidine), 2 ,6-diamino-3-[2-(benzo[b]thienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(benzo[b]thienyl)]-pyrazine), 2,4- Diamino-5-[2-(benzo[b]thienyl)]-pyrimidine (also called 3,5-diamino-6-[2-(benzo[b]thienyl)]-pyrimidine), 2,6-diamino-3 -[2-(3-chlorobenzo[b]thienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(3-chlorobenzo[b]thienyl)]-pyrazine), 2,4 -diamino-5-[2-(3-chlorobenzo[b]thienyl)]-pyrimidine (also known as 3,5-diamino-6-[2-(3-chlorobenzo[b]thienyl)]-pyrimidine) 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine; 2,6-diamino-3-(diphenylmethyl)-pyrazine; 2,4-diamino-5-(diphenylmethyl)-pyrimidine 3,5-diamino-6-(1-cyclopentyl-1-phenyl-methyl)-1,2,4-triazine; 2,6-diamino-3-(1-cyclopentyl-1-phenyl-methyl)-pyrazine 2,4-diamino-5-(1-cyclopentyl-1-phenyl-methyl)-pyrimidine; 3,5-diamino-6-[1-(6-methoxynaphthalene)methyl]-1,2,4-triazine 2,6-diamino-3-[1-(6-methoxynaphthalene)methyl]-pyrazine; 2,4-diamino-5-[1-(6-methoxynaphthalene)methyl]-pyrimidine; 3,5-diamino -6-[1-(6-methoxynaphthalene)ethyl]-1,2,4-triazine; 2,6-diamino-3-[1-(6-methoxynaphthalene)ethyl]-pyrazine; 2,4-diamino -5-[1-(6-methoxynaphthalene)ethyl]-pyrimidine; 3,5-diamino-6-(1-isopropyl-1-phenylmethyl)-1,2,4-triazine; 2,6-diamino- 3-(1-isopropyl-1-phenylmethyl)-pyrazine; 2,4-diamino-5-(1-isopropyl-1-phenylmethyl)-pyrimidine; 3,5-diamino-6-(9-xantyl)-1,2,4-triazine; 2,6-diamino-3-(9-xantyl)-pyrazine; 2,4-diamino-5-(9-xanthyl)-pyrimidine; 3,5-diamino-6-[1 , 1 bis-(4-chlorophenyl)methyl]-1,2,4-triazine; 2,6-diamino-3-[1,1 bis-(4-chlorophenyl)methyl]-pyrazine; 2,4-diamino- 5-[1,1 bis-(4-chlorophenyl)methyl]-pyrimidine; 3,5-diamino-6-[1,1-bis-(4-fluorophenyl)methyl]-1,2,4-triazine; 2,6-diamino-3-[1,1-bis-(4-fluorophenyl)methyl]-pyrazine; 2,4-diamino-5-[1,1-bis-(4-fluorophenyl)methyl]- pyrimidine; 3,5-diamino-6-{1-(4-chlorophenoxy)-1-methyl}ethyl-1,2,4-triazine; 2,6-diamino-3-{1-(4-chlorophenoxy)-1-methyl}ethyl-pyrazine; and 2,4-diamino-5-{1-(4-chlorophenoxy)-1-methyl}ethyl-pyrimidine; or salts, tautomers or solvates thereof is.

The specific pyrazine and pyrimidine compounds listed above are numbered according to the numbering used for the triazine embodiment, along with the IUPAC nomenclature. That is, the X atom is in the 1-position, the Y atom is in the 2-position, the N*-substituted C atom is in the 3-position, etc. and the A-ring substituted C atom is in the 6-position.

As Embodiment 2, the present invention provides for epilepsy, multiple sclerosis, glaucoma and uveitis, brain trauma and brain ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative diseases, motor neuron diseases, For use in the treatment of Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, neuropathic pain, migraine, bipolar disorder, mood, anxiety, cognitive disorders, schizophrenia, and trigeminal autonomic cranialgia A compound of the following formula (IA), or a salt, tautomer or solvate thereof

(wherein X is N and Y is C, or X is C and Y is N and A is a substituted 3- to 10-membered is a heterocycle, wherein the heterocycle is (i) halogen (ii) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, all optionally substituted with one or more of halogen, hydroxy, and aryl; or C1-6 alkoxy, and (iii) two or more substituents selected from amino, monosubstituted or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups; and R1 is hydrogen or a substituent selected from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl, which are any is optionally substituted with hydroxy, halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted, R2 is amino, C1 -10 alkyl or phenyl and N* is =NH if R is hydrogen or a substituent, or N* is a NRaRb group and Ra and Rb are independently H or an alkyl group or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups).

As embodiment 3, the present invention provides a compound of formula (IA), or a salt, tautomer or solvate thereof, for use as defined in embodiment 2, wherein A is thienyl or benzothienyl .

As embodiment 4, the present invention provides that A is substituted with one or more substituents selected from halogen, C1-6alkyl, C1-6alkoxy, haloC1-6alkyl and haloC1-6alkoxy, There is provided a compound of formula (IA) or a salt, tautomer or solvate thereof for use as defined in any of the previous embodiments.

As embodiment 5, the present invention provides a compound of formula (IA) for use as defined in any of the previous embodiments, wherein A is substituted with 1, 2 or 3 chlorine or bromine atoms. A compound or salt, tautomer or solvate thereof is provided.

In embodiment 6, the invention provides a compound of formula (IA), or a salt, tautomer or solvate thereof

(wherein X is N and Y is C, or X is C and Y is N and A is a substituted 3- to 10-membered is a heterocycle, wherein the heterocycle is (i) halogen, (ii) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, all optionally substituted with one or more of halogen, hydroxy, and aryl , or C1-6 alkoxy, and (iii) two or more substituents selected from amino, mono- or disubstituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl and C1-6 alkylthio groups. and R1 is hydrogen or a substituent selected from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl, any of which optionally substituted with hydroxy, halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted, R2 is amino, C1-10 alkyl or phenyl and N* is =NH if R is hydrogen or a substituent, or N* is a NRaRb group and Ra and Rb are independently H or an alkyl group or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups with the proviso that X is C, Y is N, A is halogen and optionally when it is substituted thienyl, R2 is not C1-C3 alkyl).

As embodiment 7, the present invention provides a compound of formula (I) selected from: 2,6-diamino-3-(2-thienyl)-pyrazine (also known as 3,5-diamino-6- (2-thienyl)-pyrazine), 2,4-diamino-5-(2-thienyl)-pyrimidine (also called 3,5-diamino-6-(2-thienyl)-pyrimidine), 2 ,6-diamino-3-(3-thienyl)-pyrazine (also known as 3,5-diamino-6-(3-thienyl)-pyrazine), 2,4-diamino-5-(3-thienyl) -pyrimidine (also known as 3,5-diamino-6-(3-

thienyl)-pyrimidine), 2,6-diamino-3-[3-(2,5-dichlorothienyl)]-pyrazine (also known as , 3,5-diamino-6-[3-(2,5-dichlorothienyl)]-pyrazine), 2,4-diamino-5-[3-(2,5-dichlorothienyl)]-pyrimidine (also called Also called 3,5-diamino-6-[3-(2,5-dichlorothienyl)]-pyrimidine), 2,6-diamino-3-[2-(3,4,5-trichlorothienyl)]-pyrazine (also known as 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-pyrazine), 2,4-diamino-5-[2-(3,4 ,5-trichlorothienyl)]-pyrimidine (also called 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-pyrimidine), 2(6)-amino-3- (2-thienyl)-2,3(2,5)-dihydro-6(2)-imino-5-methyl-pyrazine (also known as 5(3)-amino-6-(2-thienyl)-2, 3(2,5)-dihydro-3(5)-imino-2-methyl-pyrazine), 4(2)-amino-5-(2-thienyl)-2,3(2,5)-dihydro -2(4)-imino-1-methyl-pyrimidine (also known as 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino- 2-methyl-pyrimidine), 2(6)-amino-3-(2-thienyl)-2,3(2,5)-dihydro-6(2)-imino-5-ethyl-pyrazine (also known as , 5(3)-amino-6-(2-thienyl)-2,3(2,5)-dihydro-3(5)-imino-2-ethyl-pyrazine); 4(2)-amino-5- (2-thienyl)-2,3(2,5)-dihydro-2(4)-imino-1-ethyl-pyrimidine (also known as 5(3)-amino-6-(2-thienyl)-2, 3(2,5)-dihydro-3(5)-imino-2-ethyl-pyrimidine); 2(6)-amino-3-[3-(2,5-dichlorothienyl)]-2,3(2 ,5)-dihydro-6(2)-imino-5-methyl-pyrazine (also known as 5(3)-amino-6-[3-(2,5-dichlorothienyl)]-2,3(2, 5)-dihydro-3(5)-imino-2-methyl-pyrazine), 4(2)-amino-5-[3-(2,5-dichlorothienyl)]-2,3(2,5)-dihydro-2(4)-imino-2-methyl-pyrimidine (also known as 5(3)-amino-6-[3-(2,5-dichlorothienyl)]-2,3(2,5) -dihydro-3(5)-imino-2-methyl-pyrimidine), 2(6)-amino-3-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-6(2)-imino-5-methyl-pyrazine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2, 5)-dihydro-3(5)-imino-2-methyl-pyrazine), 4(2)-amino-5-{2-(3,4,5-trichloro)thienyl}-2,3(2 ,5)-dihydro-2(4)-imino-1-methyl-pyrimidine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2,3(2,5)-dihydro-3(5)-imino-2-methyl-pyrimidine), 2(6)-amino-3-{2-(3,4,5-trichloro)thienyl}-2,3 (2,5)-dihydro-6(2)-imino-5-ethyl-pyrazine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}-2, 3(2,5)-dihydro-3(5)-imino-2-ethyl-pyrazine), 4(2)-amino-5-{2-(3,4,5-trichloro)thienyl}-2 , 3(2,5)-dihydro-2(4)-imino-2-ethyl-pyrimidine (also known as 5(3)-amino-6-{2-(3,4,5-trichloro)thienyl}- 2,3(2,5)-dihydro-3(5)-imino-2-ethyl-pyrimidine), 2,6-diamino-3-[2-(4,5-dibromothienyl)]-pyrazine (also called Also called 3,5-diamino-6-[2-(4,5-dibromothienyl)]-pyrazine), 2,4-diamino-5-[2-(4,5-dibromothienyl)]- pyrimidine (also known as 3,5-diamino-6-[2-(4,5-dibromothienyl)]-pyrimidine), 2,6-diamino-3-[2-(5-bromothienyl)]- pyrazine (also known as 3,5-diamino-6-[2-(5-bromothienyl)]-pyrazine), 2,4-diamino-5-[2-(5-bromothienyl)]-pyrimidine (Also called 3,5-diamino-6-[2-(5-bromothienyl)]-pyrimidine), 2,6-diamino-3-[2-(3-bromothienyl)]-pyrazine (also called , 3,5-diamino-6-[2-(3-bromothienyl)]-pyrazine), 2,4-diamino-5-[2-(3-bromothienyl)]-pyrimidine (also called 3 ,5-diamino-6-[2-(3-bromothienyl)]-pyrimidine), 2,6-diamino-3-[2-(5-chlorothienyl)]-pyrazine (also called 3,5 -diamino-6-[2-(5-chlorothienyl)]-pyrazine), 2,4-diamino-5-[2-(5-chlorothienyl)]-pyrimidine (also called 3,5-diamino -6-[2-(5-chlorothienyl)]-pyrimidine), 2,6-diamino-3-[2-(benzo[b]thienyl)]-pyrazine (also called 3,5-diamino- 6-[2-(benzo[b]thienyl)]-pyrazine), 2,4-diamino-5-[2-(benzo[b]thienyl)]-pyrimidine (also called 3,5-diamino- 6-[2-(benzo[b]thienyl)]-pyrimidine), 2,6-diamino-3-[2-(3-chlorobenzo[b]thienyl)]-pyrazine (also known as 3,5- diamino-6-[2-(3-chlorobenzo[b]thienyl)]-pyrazine) and 2,4-diamino-5-[2-(3-chlorobenzo[b]thienyl)]-pyrimidine (also known as , 3,5-diamino-6-[2-(3-chlorobenzo[b]thienyl)]-pyrimidine), or salts, tautomers or solvates thereof.

The specific pyrazine and pyrimidine compounds listed above are numbered according to the numbering used for the triazine embodiment, along with the IUPAC nomenclature. That is, the X atom is in the 1-position, the Y atom is in the 2-position, the N*-substituted C atom is in the 3-position, etc. and the A-ring substituted C atom is in the 6-position.

The compounds of formula (I) have been found to inhibit interleukin-1 beta, and therefore other interleukins are useful in the treatment of many disorders and conditions.

As embodiment 8, the present invention provides a medicament comprising a compound of formula (IA) as defined in embodiment 6 or 7, or a salt, tautomer or solvate thereof, and a pharmaceutically acceptable excipient A composition is provided.

As embodiment 9, the present invention provides a compound of formula (I) as defined in embodiment 6 or 7, or a salt, tautomer or solvate thereof, for use as a medicament.

In Embodiment 10, the present invention provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, Colorectal cancer, non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, cancer metastasis in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis A therapeutically effective amount of a compound of formula (I), as defined in any one of embodiments 1-7, or a salt thereof, tautomers A method is provided comprising administering the compound or solvate to a subject in need thereof.

The present invention further provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer. , non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis, or epilepsy, multiple sclerosis, glaucoma and uveitis, brain trauma and cerebral ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, Embodiment 6 for use in treating a disorder or condition selected from neuropathic pain, migraine, bipolar disorder, mood, anxiety, cognitive disorders, schizophrenia, and trigeminal autonomic cranialgia and 7, or salts, tautomers thereof.

Compounds of formula (IB) have been found to have activity as inhibitors of interleukins 2, 4 and 13 and are therefore useful in the treatment of many diseases or conditions.

As Embodiment 11, the present invention provides that A is a group

wherein · represents a point of attachment, and R1 is hydrogen or from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl selected substituents, any of which are optionally substituted with hydroxy, halogen, carboxamido, haloC1-6 alkyl, C1-6 alkyl, or C1-6 alkoxy, or Y is N; and unsubstituted, R2 is amino, C1-10 alkyl or phenyl and R3 is phenyl, xantyl or naphthyl, each with 2 to 5 substituents selected from halogen or C1-C6 alkoxy groups and R4 is selected from hydrogen, C1-C6 alkyl, C3-C8 cycloalkyl, phenyl, xanthyl or naphthyl, wherein phenyl or naphthyl is selected from halogen or C1-C6 alkoxy groups 1- Compounds of formula (I), or salts thereof, tautomers, for uses as defined in embodiment 1, optionally substituted with 5, preferably 2 to 5, substituents and R5 is hydrogen isomers or solvates are provided.

In Embodiment 12, the present invention provides asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer, non-Hodgkin's lymphoma, melanoma, metastatic renal cancer, breast cancer, colon cancer, renal cell carcinoma, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and A compound of formula (IB) or a salt, tautomer or solvate thereof for use in treating a disease or condition selected from pulmonary tuberculosis

(wherein R3 is phenyl, xantyl or naphthyl, each optionally substituted with 1 to 5 substituents selected from halogen or C1-C6 alkoxy groups, R4 is hydrogen, C1-C6 alkyl , C3-C8 cycloalkyl, phenyl, xantyl or naphthyl, wherein phenyl or naphthyl is optionally substituted with 1 to 5, preferably 2 to 5 substituents selected from halogen or C1-C6 alkoxy groups R5 is hydrogen and R1 is hydrogen or a substituted selected from C1-10 alkyl, C2-10 alkenyl, benzyl, piperidine-methyl, thienyl-methyl, furyl-methyl or C3-10 cycloalkyl groups, any of which are optionally substituted with hydroxy, halogen, carboxamido, haloC1-6alkyl, C1-6alkyl or C1-6alkoxy, or Y is N and unsubstituted , R2 is amino, C1-10 alkyl or phenyl, N* is amino if R1 is hydrogen, =NH if R1 is a substituent, or N* is an NRaRb group; Ra and Rb are independently H or alkyl groups, or N* is a piperazinyl ring optionally substituted with one or more halogens or C1-C6 alkoxy groups.

As embodiment 12, the present invention provides that R3 is phenyl, optionally substituted with 2 or 3 substituents selected from one or more halogen, or C1-C6 alkoxy groups, and R4 is C1-C6 in embodiment 10 selected from alkyl, C3-C8 cycloalkyl, phenyl, wherein phenyl is optionally substituted with 1 to 3 substituents selected from one or more halogen or C1-C6 alkoxy groups; There is provided a compound of formula (IB), or a salt, tautomer or solvate thereof, for a defined use.

As embodiment 13, the present invention provides the compound is 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine; 3,5-diamino-6-(1-cyclopentyl-1-phenyl- methyl)-1,2,4-triazine; 3,5-diamino-6-[1-(6-methoxynaphthalene)methyl]-1,2,4-triazine; 3,5-diamino-6-[1- (6-Methoxynaphthalene)ethyl]-1,2,4-triazine;

3,5-diamino-6-(1-isopropyl-1-phenylmethyl)-1,2,4-triazine 3,5-diamino-6 -(9-xantyl)-1,2,4-triazine; 3,5-diamino-6-[1,1 bis-(4-chlorophenyl)methyl]-1,2,4-triazine; 3,5-diamino -6-[1,1-bis-(4-fluorophenyl)methyl]-1,2,4-triazine; and 3,5-diamino-6-{1-(4-chlorophenoxy)-1-methyl} a compound of formula (IB), or a salt thereof, for use as defined in embodiment 11, selected from ethyl-1,2,4-triazine; or a salt, tautomer or solvate thereof; Tautomers or solvates are provided.

The use of salts of compounds of formulas (I), (IA) and (IB) form an aspect of the invention. Preferred salts are pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable acid addition salts include both organic and inorganic acids such as hydrochloric, sulfuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, malonic, succinic, oxalic, Included are those formed with the acids fumaric acid, maleic acid, oxaloacetic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, glutamic acid, naphthoic acid, and isethionic acid. Also suitable are ethanesulfonates, malates, mandalates, benzoates, and salicylates. Base addition salts also form an aspect of the invention.

In the preparation of compounds of formula (I), (IA) or (IB), the compound or salt thereof may be obtained as a solvate of the reaction or crystallization solvent or components thereof. Use of such solvates forms another aspect of the invention. Suitable pharmaceutically acceptable solvates include hydrates.

Certain compounds of structure (I), (IA) or (IB) have chiral centers and can exist as racemates, racemic mixtures and individual enantiomers or diastereomers. All such isomers are included in the present invention. Also included within the scope of the invention are all geometric isomers of the compounds of formula (I), (IA) or (IB), either as individual isomers or as mixtures thereof. Accordingly, compounds of structure (I), (IA) or (IB) in trans and cis configurations form further aspects of the invention. Also, all other tautomeric forms of structures (I), (IA) or (IB), including mixtures thereof. In addition, some crystalline forms of compounds of structure (IA) or (IB) may exist as polymorphs, all of which are included in the present invention. Compounds of formula (IA) may be prepared by procedures analogous to those described in EP-0372934A. The reactants of formulas (II), (IV) and (V) disclosed in EP-0372934A can be replaced with the corresponding sulfur-containing heterocyclic analogues to prepare the compounds claimed herein. can be done.

Compounds of formula (IB) may be prepared according to procedures described in WO2009090431A.

The preparation of the above specific compounds is described later in this specification. Related compounds within the scope of this invention can be obtained by either explicit or routine procedures of the disclosed processes using appropriate starting materials to introduce the desired substituents and moieties of compounds within formula (IA). Modifications can be prepared.

Salts of compounds of formulas (IA) and (IB) may be obtained due to the presence of residual acid in the preparation process. Alternatively, salts are prepared by mixing a compound of formula (IA) or (IB) as a free base with a pharmaceutically acceptable acid in a suitable solvent and removing the solvent to recover the salt, or can be prepared by crystallization of In a further aspect, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt, tautomer or solvate thereof, in admixture with a pharmaceutically acceptable carrier. A pharmaceutical composition is provided for treating a disorder as detailed in the form. The compounds of formula (I) are provided in the compositions of the invention in an effective unit dosage form, ie, in an amount sufficient to be effective against the disorder in vivo.

Pharmaceutically acceptable carriers present in the compositions of the present invention can be substances conventionally used for the purpose of administering drugs. These can be liquid or solid materials that are otherwise inert or medically acceptable and compatible with the active ingredient.

These pharmaceutical compositions can be administered orally or parenterally, eg as suppositories, ointments, creams, powders or transdermal patches. However, oral administration and intravenous injection of the composition are preferred. For oral administration, fine powders or granules contain diluents, dispersants, and/or surfactants, and may include crude drugs (drafts), water or syrup, dry capsules or sachets, or suspensions. Aqueous suspensions or suspensions in water or syrups may be provided. Where desirable or necessary, flavoring, preserving, suspending, or thickening agents can be included. Dry powders or granules can be compressed to form tablets or placed in capsules. For injection, the compounds may be in sterile aqueous injectable solutions, which may contain antioxidants or buffers.

The free base or a salt or solvate thereof can also be administered in pure form without other additives, in which case capsules or sachets are preferred carriers. Alternatively, the active compound may be presented in pure

form, eg, as a compressed effective unit dose, such as a tablet. Other compounds that may be included are, for example, medically inactive ingredients such as lactose, starch, or solid and liquid diluents such as calcium phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules, Water or vegetable oils for suspensions or emulsions, lubricants such as talc or magnesium stearate, gelling agents such as colloidal clay, thickening agents such as gum tragacanth or sodium alginate, and useful as carriers for such formulations. Other therapeutically acceptable auxiliary ingredients such as wetting agents, preservatives, buffers, antioxidants and the like.

Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of a compound of formula I effective at such dosage or multiples thereof, for example units of 5 mg to 500 mg, usually Contains about 10 mg to 250 mg. A pharmaceutical composition of the present invention can be prepared by mixing a compound of formula (I) with a pharmaceutically acceptable carrier. Conventional pharmaceutical excipients can be mixed as desired. Examples of suitable formulations are provided in US Pat. No. 4,649,139, mentioned above.

The present invention relates to disorders in mammals susceptible to inhibition of interleukins, especially interleukins 1beta, 2, 4, 6, 8, 13 and 17, especially epilepsy, multiple sclerosis, glaucoma and uveitis, brain trauma. and cerebral ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, neuropathic pain, migraine, bipolar disorder, mood , anxiety and cognitive disorders, schizophrenia and trigeminal autonomic cranialgia, treatment of cancer in mammals, treatment of malaria, or asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease, Psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer, non-Hodgkin lymphoma, melanoma, metastatic kidney cancer, breast cancer, colon cancer, renal cell A method of treating disorders such as cancer, metastatic growth of cancer in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis, comprising a non-toxic and effective amount of a compound of formula (I) or its pharmaceutical or by administering a composition as defined above.

The present invention also relates to mammalian disorders susceptible to inhibition of interleukins, especially interleukins 1beta, 2, 4, 6, 8, 13 and 17, especially epilepsy, multiple sclerosis, glaucoma and uveitis, brain Trauma and brain ischemia, stroke, head trauma, spinal cord injury, surgical trauma, neurodegenerative disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, neuropathic pain, migraine, bipolar disorder, Mood, anxiety cognitive disorders, schizophrenia, trigeminal autonomic cranialgia, treatment of cancer in mammals, for treatment of malaria, or asthma, solid organ transplant rejection, atopic dermatitis, eczema, Hodgkin's disease , psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, metastatic melanoma, renal cell carcinoma, colorectal cancer, non-Hodgkin lymphoma, melanoma, metastatic kidney cancer, breast cancer, colon cancer, renal cell A compound of formula (I) or its pharmacy for the treatment of disorders such as cancer, cancer metastases in the lung and liver, chronic obstructive pulmonary disease (COPD), and pulmonary tuberculosis, or for the preparation of a medicament a pharmaceutically acceptable salt, tautomer or solvate, or composition as defined above.

As indicated above, compounds of formula (I) are generally useful in the treatment of such disorders by oral administration or intravenous injection. Compounds of formula (I) are generally administered at a dose of 0.01 mg/kg to 20 mg/kg per day, preferably 0.1 to 5.0 mg/kg per day.

Compounds of empirical formulas (I), (IA) and (IB) can be prepared according to the methods disclosed in WO2009/090431A1 using appropriate starting materials.

Example 1: 2,4-diamino-5-(diphenylmethyl)-pyrimidine

Chemical Formula: C17H16N4 Molecular Weight: 276.34 LCMS: m/z=277.20, consistent with protonated parent ion (M+H)+ 1H-NMR (DMSO-d6): 1H-NMR spectrum consistent with above structure Purities found to be: ⟩99% (by HPLC) Compounds of formulas (I), (IA) and (IB) were isolated from fresh human buffy coats by centrifugation on Lymphoprep (trademark: Stemcell Technologies) peripheral Inhibition of the proinflammatory cytokines interleukin (IL) 1β, 2, 4, 6, 8, 13 and 17A can be examined in blood mononuclear cells (PBMCs). All human cells are grown in cell culture medium RPMI-1640 supplemented with 1% penicillin/streptomycin and 5% heat-inactivated fetal bovine serum.

PBMCs stimulated with LPS (Salmonella enterica serovar Typhimurium) are incubated with the compound under study for 24 hours and reconstituted with dimethylsulfoxide (DMSO). Levels of secreted interleukin-1β are measured in cell culture supernatants using cytometric bead arrays and trypan blue is used to quantify cell viability.

PMA/ionomycin-stimulated PBMC are incubated with the compound under study for 24 hours and reconstituted with DMSO. Interleukin 17A secretion levels are measured in cell culture supernatants using a cytometric bead array and cell viability is quantified using trypan blue.

Compounds of formulas (I), (IA) and (IB) inhibit the proinflammatory cytokine interleukin activity in human CD4+ T cells isolated from freshly isolated PBMCS using a CD4+ T cell isolation kit. 2, 4 and 13 can be examined for inhibition. CD4-positive T cells stimulated with antibody-coated beads against CD2, CD3, and CD28 are incubated with the compound under study for 48 hours and reconstituted with DMSO. Secreted levels of interleukins 2, 4, and 13 were measured in cell culture supernatants using cytometric bead arrays, and cell viability was measured using MTT (3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide) assay. Secreted IL-4 levels can be measured using electrochemiluminescence (MSD kit, Meso Scale Discovery), whereas secreted IL-2 levels can be measured using proximity homogeneous time-resolved fluorescence (HTRF). can be measured and the amount of viable cells can be measured by addition of resazurin (PrestoBlue®).

The compound 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine was studied using the methods described above and showed interleukin IL-17A and IL- 8 and moderate inhibition of IL-1β and IL-6.

３，５－ジアミノ－６－（ジフェニルメチル）－１，２，４－トリアジン：

3,5-Diamino-6-(diphenylmethyl)-1,2,4-triazine can be prepared by the process disclosed in WO2009/090431A1.

3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine exhibits relative EC50s of 28.0 and 50.5 nM when tested in the IL-2 and IL-4 inhibition assays, respectively. I found out.

These data demonstrate good levels of both IL-2 and IL-4 by 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine without significant inhibition of cell viability. have demonstrated inhibition of

Further data are shown in the figure. FIG. 1 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL)-1 beta, bar indicates the mean±SEM for n=9-10 subjects.

FIG. 2 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL)-6, bars Shown is the mean±SEM for n=9-10 subjects.

FIG. 3 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazine on interleukin (IL)-8, bars Shown is the mean±SEM for n=8-12 subjects.

FIG. 4 shows the inhibitory effect of 3,5-diamino-6-[2-(3,4,5-trichlorothienyl)]-1,2,4-triazinone on interleukin (IL)-17A, bar indicates the mean±SEM for n=5-7 subjects.

FIG. 5 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4-triazine on interleukin (IL)-17A, bars n=9-12 subjects. Mean ± SEM for examiner is shown.

FIG. 6 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4- on interleukin (IL)-8, bars mean for n=5-8 subjects. ±SEM are shown.

FIG. 7 shows the inhibitory effect of 3,5-diamino-6-(diphenylmethyl)-1,2,4- on interleukin (IL)-6, bars mean for n=9-10 subjects. ±SEM are shown.