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(54) **Title:**
NEW CRYSTALLINE FORM OF A CYCLOPROPYL BENZAMIDE DERIVATIVE

(57) **Abstract:**
The present invention relates to a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, (I) pharmaceutical formulations containing said compound and to the use of said active compound in therapy.

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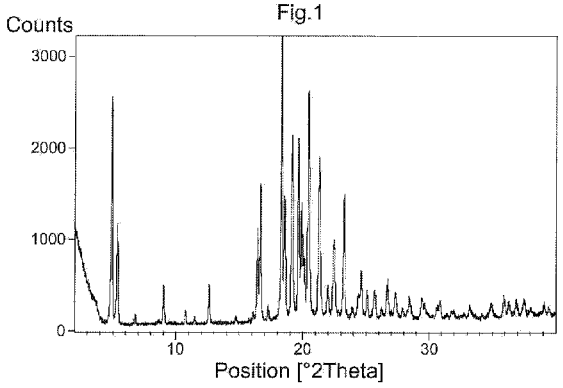
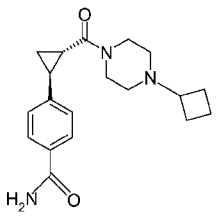
(57) Abstract: The present invention relates to a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, (I) pharmaceutical formulations containing said compound and to the use of said active compound in therapy.

Fig.1





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NEW CRYSTALLINE FORM OF A CYCLOPROPYL BENZAMIDE DERIVATIVE

FIELD OF THE INVENTION

The present invention relates to crystalline forms of a compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, particularly such as Form I, pharmaceutical formulations containing said compound and to the use of said active compounds in therapy.

BACKGROUND OF THE INVENTION

The crystalline forms of 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide are useful to treat at least one histamine H3 receptor associated condition.

The histamine H3 receptor is of current interest in developing new medicaments. The H3 receptor is a presynaptic autoreceptor located both in the central and peripheral nervous systems, the skin, and in organs, such as, for example, the lung, the intestine, probably the spleen, and the gastrointestinal tract. Recent evidence suggests the H3 receptor has intrinsic, constitutive activity *in vitro* as well as *in vivo* (i.e., it is active in the absence of an agonist). Compounds acting as inverse agonists can inhibit this activity. The histamine H3 receptor has been shown to regulate the release of histamine and also of other neurotransmitters, such as, for example, serotonin and acetylcholine. Some histamine H3 ligands, such as, for example, a histamine H3 receptor antagonist or inverse agonist may increase the release of neurotransmitters in the brain, whereas other histamine H3 ligands, such as, for example, histamine H3 receptor agonists may inhibit the biosynthesis of histamine, as well as, inhibit the release of neurotransmitters. This suggests that histamine H3 receptor agonists, inverse agonists, and antagonists could mediate neuronal activity. As a result, efforts have been undertaken to develop new therapeutics that target the histamine H3 receptor.

WO2009/024823 describes the synthesis of a number of cyclopropyl amide derivatives, such as, for example, 4-((trans)-2-[(4-cyclobutylpiperazin-yl)carbonyl]-cyclopropyl}-benzamide (enantiomer 1; Example 43).

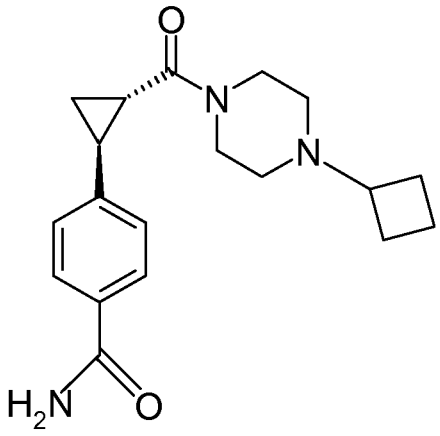
DETAILED DESCRIPTION OF THE INVENTION

One object of the present invention is to provide crystalline forms of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide.

Another object of the present invention is to provide a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, as Form I.

Said compound (I) having a histamine receptor antagonist or inverse agonist effect at the H3 receptor which making them suitable to be formulated into pharmaceutical formulations.

Accordingly, the present invention provides a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide



(I).

One aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with at least one peak at about 18.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

Another aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with at least two peaks at about 4.9 and

about 18.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

Yet another aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with at least three peaks at about 4.9, about 18.3 and about 20.4 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

Still another aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with at least four peaks at about 4.9, about 18.3, about 19.6 and about 20.4 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

A further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at selected °2Theta-values described above and with additional peaks at about 16.4 and about 16.6, °2Theta when measured using radiation with a wavelength of about 1.54 angstroms.

Yet a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at selected °2Theta-values described above and with an additional peak at about 5.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

Still a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at °2Theta-values selected from about 4.9, about 16.4, about 16.6, about 18.3, about 19.6 and about 20.4, when measured using radiation with a wavelength of about 1.54 angstroms.

Still a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at °2Theta-values selected from about 4.9, about 5.3, about 16.4, about 16.6, about 18.3, about 19.6 and about 20.4, when measured using radiation with a wavelength of about 1.54 angstroms.

Still a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at °2Theta-values selected from about 4.9, about 12.6, about 16.4, about 16.6, about 18.3, about 19.6, about 20.4, and about 23.2, when measured using radiation with a wavelength of about 1.54 angstroms.

Still a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at °2Theta-values selected from about 4.9, about 5.3, about 9.0, about 12.6, about 16.4, about 16.6, about 18.3, about 19.6, about 20.4, and about 23.2, when measured using radiation with a wavelength of about 1.54 angstroms.

Still a further aspect of the invention relates to a crystalline form of compound (I), characterized in that said form has an XRDP pattern (Cu Kα) with peaks at from about 4.9, about 5.3, about 9.0, about 12.6, about 16.4, about 16.6, about 18.3, about 19.6, about 20.4, about 21.2, about 23.2 and about 24.6 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

Yet still a further aspect of the invention relates to relates to a crystalline form of compound (I), characterized by the X-ray powder diffraction pattern essentially as shown in Figure 1.

Another embodiment relates to a crystalline form of compound (I) that has a DSC thermogram essentially as depicted in Figure 2.

In another embodiment, a crystalline form of compound (I) has a DSC thermogram comprising an endothermic event with an onset temperature of about 225°C.

In still another embodiment, a crystalline form of compound (I) has a DSC thermogram comprising an endothermic event with a peak temperature of about 235°C.

It is well known that the DSC onset and peak temperatures as well as energy values may vary due to, for example, the purity of the sample and sample size and due to instrumental parameters, especially the temperature scan rate. Hence the DSC data presented are not to be taken as absolute values. A person skilled in the art can set up instrumental parameters for a Differential scanning calorimeter so that data comparable to the data presented here can be collected according to standard methods, for example those described in Höhne, G. W. H. *et al* (1996), Differential Scanning Calorimetry, Springer, Berlin.
The crystalline forms of compound (I) of the present invention may also exist as solvates, including hydrates.

The present invention also relates to the use of a crystalline form of compound (I), as hereinbefore defined.

A crystalline form of compound (I), as hereinbefore defined has one or more advantageous properties. For example, in some embodiments, a crystalline form of compound (I) shows advantageous properties, such as, for example, a high melting point, a substantial lack of solvent (e.g., water) content, little or no weight loss on heating, and/or low hygroscopicity. In certain embodiments, such properties advantageously facilitate the manufacture, storage, formulation, and/or delivery of compound (I).
A crystalline form of compound (I), as described herein, for example Form I of compound (I) provide advantageous properties with regard to stability.

A substance can be expected to be more stable chemically in a crystalline state in comparison with the same substance in an amorphous state, as described in Haleblian and McCrone J. Pharm. Sci 1969, 58, pages 911-929, especially page 913. This observation is common for small molecules (i.e. non-proteins) but not always true for macromolecules like proteins, as described in Pikal and Rigsbee, Pharm. Res. 1997, 14, pages 1379-1387, especially page 1379. A crystalline state is thus beneficial for small molecules such as compound (I).

X-rays will be scattered by electrons in atoms in a substance. Crystalline material will diffract X-rays giving peaks in directions of constructive interference. The directions are

determined by the crystal structure, including the size and shape of the unit cell. All diffraction peak °2Theta values disclosed and / or claimed herein refer to Cu Kα-radiation. An amorphous (non-crystalline) material will not give such diffraction peaks. See e.g. Klug, H. P. & Alexander, L. E., X-Ray Diffraction Procedures For Polycrystalline and Amorphous Materials, 1974, John Wiley & Sons.

The ability for a compound to lump together or cake without control will increase if the compound is heated to near its melting temperature. Lumps and cakes will have different flow and dissolution properties as compared with a powder. Mechanical treatment of a powder, such as during particle size reduction, will bring energy into the material and thus give a possibility to raise the temperature. Storage of a compound as well as transport of a compound can unintentionally also lead to an increased temperature. Melting is an endothermic event. Endothermic events can be measured by, e.g. differential scanning calorimetry (DSC).

It is thus beneficial for a compound of formula (I) or a pharmaceutically acceptable salt thereof salt thereof to have such endothermic events at a temperature higher than the highest temperature expected during normal use to prevent said compounds from forming an undesired lump or cake.

PHARMACEUTICAL FORMULATIONS

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising a crystalline form of the compound (I), such as Form I, for use in the prevention and/or treatment of conditions associated with the H3 receptor.

The formulation used in accordance with the present invention may be in a form suitable for oral administration, for example such as a tablet, pill, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for topical administration for example such as an ointment, patch or cream, for rectal administration for example such as a suppository and for other non-parenteral administration.

Suitable daily doses a crystalline form of the compound (I), such as Form I, in the treatment of a mammal, including human, are approximately 0.01 to 250 mg/kg bodyweight at per oral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

A crystalline form of compound (I), such as for example Form I, may be used on its own but will usually be administered in the form of a pharmaceutical formulation in which the active ingredient is in association with pharmaceutically acceptable diluents, excipients and/or inert carrier known to a person skilled in the art. Dependent on the mode of administration, the pharmaceutical formulation may comprise from 0.05 to 99 %w (per cent by weight), for example from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The invention further provides a process for the preparation of a pharmaceutical formulation of the invention which comprises mixing of a crystalline form of the compound (I), such as form I, as hereinbefore defined, with pharmaceutically acceptable diluents, excipients and/or inert carriers.

MEDICAL USES

In one embodiment, at least one crystalline form of the compound (I) described herein may be administered to a mammal, including human, to be used to modulate at least one histamine H3 receptor. The terms “modulate”, “modulates”, “modulating”, or "modulation", as used herein, refer to, for example, the activation (e.g., agonist activity) or inhibition (e.g., antagonist and inverse agonist activity) of at least one histamine H3 receptor. In one embodiment, at least one crystalline form of the compound (I) described herein may be administered to a mammal, including human, to be used as an inverse agonist of at least one histamine H3 receptor. In another embodiment, at least one crystalline form of the compound (I) described herein may be administered to a mammal, including human, to be used as an antagonist of at least one histamine H3 receptor. In

another embodiment, at least one crystalline form of the compound (I) described herein may be used as an antagonist of at least one histamine H3 receptor. In yet another embodiment, at least one crystalline form of the compound (I) described herein may be used an antagonist of at least one histamine H3 receptor.

At least one crystalline form of the compound (I) described herein may be administered to a mammal, including human, to be used to treat one or more of a wide range of conditions or disorders in which modulating the histamine H3 receptor is beneficial. At least one crystalline form of the compound (I) described herein may administered to a mammal, including human, to be, for example, be useful to treat at least one disease of the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system, or the endocrinological system.

Another embodiment provides a method for treating a disorder in which modulating the function of at least one histamine H3 receptor is beneficial comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of crystalline form of the compound (I).

One embodiment relates to the use of the crystalline form of a compound (I) in the manufacture of a medicament for the treatment of at least one disorder selected from schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, Alzheimer's disease, cognition deficiency, and cognition deficiency associated with schizophrenia.

A further embodiment relates to a method for the therapy of at least one disorder selected from schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, Alzheimer's disease, cognition deficiency, and cognition deficiency associated with schizophrenia, in a warm-blooded animal in need of such therapy, wherein the method comprises administering to the animal a therapeutically effective amount of a crystalline form of the compound (I).

A crystalline form of the compound (I) may be useful to treat at least one autoimmune disorder. Exemplary autoimmune disorders include, but are not limited to, for example, arthritis, skin grafts, organ transplants and similar surgical needs, collagen diseases, various allergies, tumors and viruses.

A crystalline form of the compound (I) may be useful to treat at least one psychiatric disorder.

Exemplary psychiatric disorders include, but are not limited to, for example, Psychotic Disorder(s) and Schizophrenia Disorder(s), such as, for example, Schizoaffective Disorder(s), Delusional Disorder(s), Brief Psychotic Disorder(s), Shared Psychotic Disorder(s), and Psychotic Disorder(s) Due to a General Medical Condition; Dementia and other Cognitive Disorder(s); Anxiety Disorder(s), such as, for example, Panic Disorder(s) Without Agoraphobia, Panic Disorder(s) With Agoraphobia, Agoraphobia Without History of Panic Disorder(s), Specific Phobia, Social Phobia, Obsessive-Compulsive Disorder(s), Stress related Disorder(s), Posttraumatic Stress Disorder(s), Acute Stress Disorder(s), Generalized Anxiety Disorder(s) and Generalized Anxiety Disorder(s) Due to a General Medical Condition; Mood Disorder(s), such as, for example, a) Depressive Disorder(s) (including but not limited to, for example, Major Depressive Disorder(s) including depression, major depression, mood stabilization and/or apathy, and Dysthymic Disorder(s)), b) Bipolar Depression and/or Bipolar mania, such as, for example, Bipolar I (which includes, but is not limited to those with manic, depressive or mixed episodes), Bipolar II, and Bipolar Maintenance, c) Cyclothymiac's Disorder(s), and d) Mood Disorder(s) Due to a General Medical Condition; Sleep Disorder(s), such as, for example, excessive daytime sleepiness, narcolepsy, hypersomina, and sleep apnea; Disorder(s) Usually First Diagnosed in Infancy, Childhood, or Adolescence including, but not limited to, for example, Mental Retardation, Down´s Syndrome, Learning Disorder(s), Motor Skills Disorder(s), Communication Disorders(s), Pervasive Developmental Disorder(s), Attention-Deficit and Disruptive Behavior Disorder(s), Feeding and Eating Disorder(s) of Infancy or Early Childhood, Tic Disorder(s), and Elimination Disorder(s); Substance-Related Disorder(s) including, but not limited to, for example, Substance Dependence, Substance Abuse, Substance Intoxication, Substance Withdrawal, Alcohol-Related Disorder(s), Amphetamines (or Amphetamine-Like)-Related Disorder(s), Caffeine-Related

Disorder(s), Cannabis-Related Disorder(s), Cocaine-Related Disorder(s), Hallucinogen-Related Disorder(s), Inhalant-Related Disorder(s), Nicotine-Related Disorder(s), Opiod-Related Disorder(s), Phencyclidine (or Phencyclidine-Like)-Related Disorder(s), and Sedative-, Hypnotic- or Anxiolytic-Related Disorder(s); Attention-Deficit and Disruptive Behavior Disorder(s); Eating Disorder(s), such as, for example, obesity; Personality Disorder(s) including, but not limited to, for example, Obsessive-Compulsive Personality Disorder(s); Impulse-Control Disorder(s); Tic Disorders including, but not limited to, for example Tourette's Disorder, Chronical Tics Syndrome, Chronic motor or vocal tic disorder; and Transient Tic Disorder. At least one of the above psychiatric disorders is defined, for example, in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000.

A crystalline form of the compound (I) may be useful: i) to treat obesity or being overweight (e.g., promotion of weight loss and maintenance of weight loss), eating disorders (e.g., binge eating, anorexia, bulimia and compulsive), and/or cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items); ii) to prevent weight gain (e.g., medication-induced or subsequent to cessation of smoking); and/or iii) to modulate appetite and/or satiety. At least one solid form described herein may be suitable for treating obesity by reducing appetite and body weight and/or maintaining weight reduction and preventing rebound. At least one solid form described herein may be used to prevent or reverse medication-induced weight gain, e.g., weight gain caused by antipsychotic (neuroleptic) treatment(s); and/or weight gain associated with smoking cessation.

A crystalline form of the compound (I) may be useful to treat at least one Neurodegenerative Disorder.

Exemplary Neurodegenerative Disorders include, but are not limited to, for example, conditions associated with cognitive disorder(s) or indications with deficit(s) in cognition such as: dementia; incl. pre-senile dementia (early onset Alzheimer's Disease); senile dementia (dementia of the Alzheimer's type); Alzheimer's Disease (AD); Familial Alzheimer's disease; Early Alzheimer's disease; mild to moderate dementia of the

Alzheimer's type; delay of disease progression of Alzheimer's Disease; neurodegeneration associated with Alzheimer's disease, Mild Cognitive Impairment (MCI); Amnestic Mild Cognitive Impairment (aMCI); Age-associated Memory Impairment (AAMI); Lewy body dementia; vascular dementia (VD); HIV-dementia; AIDS dementia complex; AIDS - Neurological Complications; Frontotemporal dementia (FTD); Frontotemporal dementia Parkinson's Type (FTDP); dementia pugilistica; dementia due to infectious agents or metabolic disturbances; dementia of degenerative origin; dementia - Multi-Infarct; memory loss; cognition in Parkinson's Disease; cognition in multiple sclerosis; cognition deficits associated with chemotherapy; Cognitive Deficit in Schizophrenia (CDS); Schizoaffective disorders including schizophrenia; Age-Related Cognitive Decline (ARCD); Cognitive Impairment No Dementia (CIND); Cognitive Deficit arising from stroke or brain ischemia; Congenital and/or development disorders; progressive supranuclear palsy (PSP); amyotrophic lateral sclerosis (ALS); corticobasal degeneration(CBD); traumatic brain injury (TBI); postencephelatic parkinsonism; Pick's Disease; Niemann-Pick's Disease; Down's syndrome; Huntington's Disease; Creuztfeld-Jacob's disease; prion diseases; multiple sclerosis (MS); motor neuron diseases (MND); Parkinson's Disease (PD); β-amyloid angiopathy; cerebral amyloid angiopathy; Trinucleotide Repeat Disorders; Spinal Muscular Atrophy; Ataxia; Friedreich's Ataxia; Ataxias and Cerebellar or Spinocerebellar Degerneration ;Neuromyelitis Optica; Multiple System Atrophy; Transmissible Spongiform Encephalopathies; Attention Deficit Disorder (ADD); Attention Deficit Hyperactivity Disorder (ADHD); Bipolar Disorder (BD) including acute mania, bipolar depression, bipolar maintenance; Major Depressive Disorders (MDD) including depression, major depression, mood disorder (stabilization), dysthymia and apathy; Guillain-Barré Syndrome (GBS); and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

A crystalline form of the compound (I) may be useful to treat at least one Neuroinflammatory Disorder including, but not limited to, for example, Multiple Sclerosis (MS), which includes, but is not limited to, for example, Relapse Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS); Parkinson's disease; Multiple System Atrophy

(MSA); Corticobasal Degeneration; Progressive Supranuclear Paresis; Guillain-Barré Syndrome (GBS); and chronic inflammatory demyelinating polyneuropathy (CIDP).

A crystalline form of the compound (I) may be useful to treat at least one Attention-Deficit and Disruptive Behavior Disorder.
Exemplary Attention-Deficit and Disruptive Behavior Disorders include, but are not limited to, for example, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and affective disorders.

A crystalline form of the compound (I) may be useful to treat pain, including acute or chronic pain disorders including but not limited to, for example, Widespread pain, Localized pain, Nociceptive pain, Inflammatory pain, Central pain, Central and peripheral neuropathic pain, Diabetic neuropathic pain, Central and peripheral neurogenic pain, Central and peripheral neuralgia, Low back pain, Postoperative pain, Visceral pain, and Pelvic pain; Allodynia; Anesthesia dolorosa; Causalgia; Dysesthesia; Fibromyalgia; Hyperalgesia; Hyperesthesia; Hyperpathia; Ischemic pain; Sciatic pain; Burn-induced pain; Pain associated with cystitis including, but not limited to, interstitial cystitis; Pain associated with multiple sclerosis; Pain associated with arthritis; Pain associated with osteoarthritis; Pain associated with rheumatoid arthritis; Pain associated with pancreatitis; Pain associated with psoriasis; Pain associated with fibromyalgia; Pain associated with IBS; Pain associated with cancer; and Restless Legs Syndrome.

A crystalline form of the compound (I) may be useful to treat at least one of the following disorders Autism, Dyslexia, Jetlag, Hyperkinesias, Dystonias, Rage outbursts, Muscular Dystrophy, Neurofibromatosis, Spinal Cord Injury, Cerebral Palsy, Neurological Sequelae of Lupus and Post-Polio Syndrome.

A crystalline form of the compound (I) may be used for the manufacture of a medicament for the treatment of at least one autoimmune disorder, psychiatric disorder, obesity disorder, eating disorder, craving disorder, neurodegenerative disorder, neuroinflammatory disorder, Attention-Deficit and Disruptive Behaviour Disorder, and/or pain disorder described hereinabove.

A crystalline form of the compound (I) may be used for the treatment of at least one disorder selected from cognitive deficits in schizophrenia and Alzheimer's disease. One embodiment of the invention relates to the prevention and/or treatment of Alzheimer's Disease, especially the use in symptomatic treatment of mild to moderate Alzheimer's Disease or in the treatment of mild to moderate dementia of Alzheimer type.

Other embodiments of the invention relate to the prevention and/or treatment of disorders selected from the group consisting of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and affective disorders, wherein the affective disorders are Bipolar Disorder including acute mania, bipolar depression, bipolar maintenance, major depressive disorders (MDD) including depression, major depression, mood stabilization, schizoaffective disorders including schizophrenia, and dysthymia.

Another aspect provides a method for treating at least one autoimmune disorder, psychiatric disorder, obesity disorder, eating disorder, craving disorder, neurodegenerative disorder, neuroinflammatory disorder, attention-deficit and disruptive behaviour disorder, and/or pain disorder in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet another aspect provides a method for treating at least one disorder selected from cognitive deficits in schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, and Alzheimer's disease in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet another aspect provides a method for treating cognitive deficits in schizophrenia in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet another aspect provides a method for treating obesity in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet another aspect provides a method for treating narcolepsy in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet another aspect provides a method for treating excessive daytime sleepiness in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

One embodiment of the invention relates to the prevention and/or treatment of Alzheimer's Disease, especially the use in the delay of the disease progression of Alzheimer's Disease.

Other embodiments of the invention relate to the prevention and/or treatment of disorders selected from the group consisting of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and affective disorders, wherein the affective disorders are Bipolar Disorder including acute mania, bipolar depression, bipolar maintenance, major depressive disorders (MDD) including depression, major depression, mood stabilization, schizoaffective disorders including schizophrenia, and dysthymia.

Still another aspect provides a method for treating Alzheimer's disease in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Still yet another aspect provides a method for treating attention deficit hyperactivity disorder in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet still another aspect provides a method for treating a pain disorder in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

Yet still another aspect provides a method for treating neuropathic pain in a warm-blooded animal, comprising administering to said animal in need of such treatment a therapeutically effective amount of a crystalline form of the compound (I).

In one embodiment, the warm-blooded animal is a mammalian species including, but not limited to, for example, humans and domestic animals, such as, for example, dogs, cats, and horses. In one embodiment, the warm-blooded animal is a human.

Another aspect provides the use of a crystalline form of the compound (I) in therapy.

Another embodiment provides the use of a crystalline form of the compound (I) in the manufacture of a medicament for use in therapy.

Another aspect of the invention is wherein a compound of formula (I) as defined herein, or a pharmaceutical composition or formulation comprising a combination comprising such a compound of formula (I) is administered, concurrently, simultaneously, sequentially, separately or adjunct with another pharmaceutically active compound or compounds selected from the following:

(i) antidepressants including for example agomelatine, amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, ramelteon, reboxetine, robalzotan, sertraline, sibutramine, thionisoxetine, tranylcypromaine, trazodone, trimipramine, venlafaxine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(ii) atypical antipsychotics including for example quetiapine and pharmaceutically active isomer(s) and metabolite(s) thereof;

(iii) antipsychotics including for example amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, loxapine, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclone, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(iv) anxiolytics including for example alnespirone, azapirones,benzodiazepines, barbiturates such as adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, quazepam, reclazepam, tracazolate, trepipam, temazepam, triazolam, uldazepam, zolazepam and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(v) anticonvulsants including for example carbamazepine, clonazepam, ethosuximide, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabaline, rufinamide, topiramate, valproate, vigabatrine, zonisamide, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(vi) Alzheimer´s therapies including for example donepezil, rivastigmine, galantamine, memantine, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(vii) Parkinson's therapies including for example levodopa, dopamine agonists such as apomorphine, bromocriptine, cabergoline, pramipexol, ropinirole, and rotigotine, MAO-B inhibitors such as selegeline and rasagiline, and other dopaminergics such as tolcapone and entacapone, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, and inhibitors of neuronal nitric oxide synthase and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(viii) migraine therapies including for example almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, dihydroergotamine, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pizotiphen, pramipexole, rizatriptan,

ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(ix) stroke therapies including for example thrombolytic therapy with eg activase and desmoteplase, abciximab, citicoline, clopidogrel, eptifibatide, minocycline, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(x) urinary incontinence therapies including for example darafenacin, falvoxate, oxybutynin, propiverine, robalzotan, solifenacin, tolterodine and and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xi) neuropathic pain therapies including lidocain, capsaicin, and anticonvulsants such as gabapentin, pregabalin, and antidepressants such as duloxetine, venlafaxine, amitriptyline, klomipramine, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xii) nociceptive pain therapies including paracetamol, NSAIDS and coxibs, such as celecoxib, etoricoxib, lumiracoxib, valdecoxib, parecoxib, diclofenac, loxoprofen, naproxen, ketoprofen, ibuprofen, nabumeton, meloxicam, piroxicam and opioids such as morphine, oxycodone, buprenorfin, tramadol and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xiii) insomnia therapies including for example agomelatine, allobarbital, alonimid, amobarbital, benzoctamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, ethchlorvynol, etomidate, glutethimide, halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midaflur, nisobamate, pentobarbital, phenobarbital, propofol, ramelteon, roletamide, triclofos,secobarbital, zaleplon, zolpidem and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xiv) mood stabilizers including for example carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, verapamil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xv) obesity therapies, such as, for example, anti-obesity drugs that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms,

appetite/motivation, food intake, and G-I motility; very low calorie diets (VLCD); and low-calorie diets (LCD);

(xvi) therapeutic agents useful in treating obesity associated disorders, such as, for example, biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors), PPAR modulating agents, such as, for example, PPAR alpha and/or gamma agonists; sulfonylureas; cholesterol-lowering agents, such as, for example, inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase); an inhibitor of the ileal bile acid transport system (IBAT inhibitor); a bile acid binding resin; bile acid sequestering agent, such as, for example, colestipol, cholestyramine, or cholestagel; a CETP (cholesteryl ester transfer protein) inhibitor; a cholesterol absorption antagonist; a MTP (microsomal transfer protein) inhibitor; a nicotinic acid derivative, including slow release and combination products; a phytosterol compound; probucol; an anti-coagulant; an omega-3 fatty acid; an anti-obesity therapy, such as, for example, sibutramine, phentermine, orlistat, bupropion, ephedrine, and thyroxine; an antihypertensive, such as, for example, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic, and a vasodilator; a melanin concentrating hormone (MCH) modulator; an NPY receptor modulator; an orexin receptor modulator; a phosphoinositide-dependent protein kinase (PDK) modulator; modulators of nuclear receptors, such as, for example, LXR, FXR, RXR, GR, ERRα, β, PPARα, β, γ and RORalpha; a monoamine transmission-modulating agent, such as, for example, a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NARI), a noradrenaline-serotonin reuptake inhibitor (SNRI), a monoamine oxidase inhibitor (MAOI), a tricyclic antidepressive agent (TCA), a noradrenergic and specific serotonergic antidepressant (NaSSA); a serotonin receptor modulator; a leptin/leptin receptor modulator; a ghrelin/ghrelin receptor modulator; a DPP-IV inhibitor; and equivalents and pharmaceutically active isomer(s), metabolite(s), and pharamaceutically acceptable salts, solvates, and prodrugs thereof;

(xvii) agents for treating ADHD, such as, for example, amphetamine, methamphetamine, dextroamphetamine, atomoxetine, methylphenidate,

dexmethylphenidate, modafinil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; and

(xviii) agents used to treat substance abuse disorders, dependence, and withdrawal, such as, for example, nicotine replacement therapies (i.e., gum, patches, and nasal spray); nicotinergic receptor agonists, partial agonists, and antagonists, (e.g., varenicline); acomprosate, bupropion, clonidine, disulfiram, methadone, naloxone, naltrexone, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

The dose required for the therapeutic or preventive treatment of a particular disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

For veterinary use the amounts of different components, the dosage form and the dose of the medicament may vary and will depend on various factors such as, for example the individual requirement of the animal treated.

When employed in combination with at least one solid form described herein, the above other pharmaceutically active compound may be used, for example, in the amounts indicated in the Physicians' Desk Reference (PDR; e.g., 64th ed. 2010) or approved dosage ranges and/or dosage described in published references or as otherwise determined by one of ordinary skill in the art.

Dosages can be readily ascertained by those skilled in the art based on this disclosure and the knowledge in the art. Thus, the skilled person can readily determine the amount of crystalline form and optional additives, vehicles, and/or carriers in compositions and to be administered in methods provided herein. The specific dose level and frequency of dosage for any particular subject, however, may vary and generally depends on a variety of factors, including, but not limited to, for example, the dissolution and/or bioavailability of the solid form(s) described herein; species, age, body weight, general health, sex, and diet of the subject; mode and time of administration; rate of excretion; drug combination; and severity of the particular condition.

In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

In the context of the present specification, the term "disorder" also includes "condition" unless there are specific indications to the contrary.

In one embodiment of the invention the combination comprises the group of compounds (a) and (b) as defined below:

(a) a first therapeutic agent, which is a H3 inhibitor and (b) a second therapeutic agent, which is a NMDA-receptor antagonist selected from:
(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, such as for example Form I, and (b) a second therapeutic agent, which is memantine;

(a) a first therapeutic agent, which is a H3 antagonist or inverse agonist and (b) a second therapeutic agent, which is a acetyl choline esteras inhibitor.
(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, such as for example Form I, and (b) a second therapeutic agent, which is a donepezil.
(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, such as for example Form I, and (b) a second therapeutic agent, which is a rivastigmine.
(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, such as for example Form I, and (b) a second therapeutic agent, which is a galantamine.

(a) a first therapeutic agent, which is a H3 inhibitor and (b) a second therapeutic agent, which is a voltage-gated calcium channel inhibitor selected from:

(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, such as for example Form I, and (b) a second therapeutic agent, which is pregabalin.

(a) a first therapeutic agent, which is a crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide , such as for example Form I, and (b) a second therapeutic agent, which is gabapentin.

Such combination products employ the compound of this invention within the dosage range described herein and the other pharmaceutically active compound or compounds within approved dosage ranges and/or the dosage described in the publication reference.

METHODS OF PREPARATION

A process for the preparation of a crystalline form of a compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, Form I, are described in comprising the following steps:

a) dissolving (1*S*, 2*S*)-2-(4-Carbamoyl-phenyl)-cyclopropanecarboxylic acid and cyclobutylpiperazine or a suitable salt thereof (for example the dihydrochloride) in a suitable solvent such as DMSO in the presence of a base such as N-methylmorpholine;

b) adding an activating agent such as a mixture of 1-hydroxybenzotriazole / N-methylmorpholine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in a suitable solvent such as DMSO; followed by

c) heating the solution to 60°C and adjusting pH to about 8 with a base such as an trialkylamine for example triethylamine; followed by

d) cooling to 20°C, adding water and let to stirring for 16 hr.; followed by

e) filtering off the product; followed by

f) slurry washing with cold water; followed by

g) drying the obtained solid under vacuum at 40°C

to obtain a crystalline Form I of compound (I).

Alternatively, the compound of formula (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, dissolved or as a slurry of amorphous material,

may be crystallised in a suitable solvent, such as, for example dimethylsulfoxide (DMSO), water or mixtures thereof. Other suitable solvents for crystallisation are lower alcohols, such as, for example, methanol, ethanol, 1-propanol, 2-propanol. 1-butanol and water or mixtures thereof.

Crystallization of the compound of formula (I) from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent system by solvent evaporation, by temperature decrease, and/or via the addition of antisolvent (i.e. a solvent in which the compounds of the invention are poorly soluble) and/or by a chemical reaction. An example of a suitable solvent is DMSO and an example of a suitable antisolvent is water.

Crystallisation temperatures and times depend upon the concentration in the solution and the solvent system used.

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline compound of the invention.

The crystalline form of a compounds of formula (I) may be isolated using techniques, which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

The crystalline form of a compounds of formula (I) may be dried using standard techniques, which are well known to those skilled in the art.

Alternatively, a crystalline form of compound of formula (I) may be further purified by column chromatography on silica eluting with a suitable organic solvent or a mixture of solvents, such as for example mixtures of dichloromethane and methanol optionally containing ammonia in methanol.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows an X-ray powder diffractogram (XRDP) pattern for Form I of Compound (I).

Figure 2 shows a differential scanning calorimetry (DSC) thermogram for Form I of Compound (I).

WORKING EXAMPLES

The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below, but rather defined by the claims appended hereto.

All temperatures are in degrees Celsius (°C) and are uncorrected.

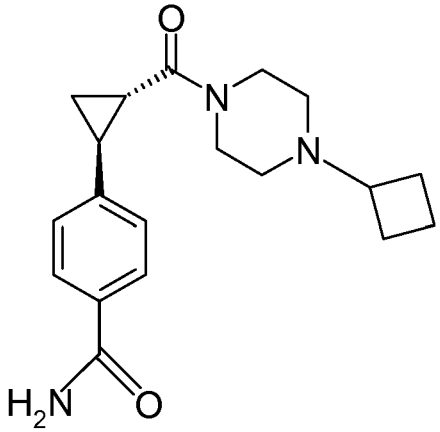
Unless otherwise noted, commercial reagents used in preparing the example compounds were used as received without additional purification.

Unless otherwise noted, the solvents used in preparing the example compounds were commercial anhydrous grades and were used without further drying or purification.

Compounds used as starting materials in the Example and Methods are commercially available otherwise a process for preparing them are described in the Intermediates A-F herein.

Example 1

4-{(1S, 2S)-2-[(4-Cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide, Form I



First Method

Intermediate E (5.52 g, 26.7 mmoles, 99.1% w/w) and Intermediate F (6.07 g, 28.0 mmoles, 98.40% w/w) were mixed in DMSO (82mL) at t_{jacket}=22°C. N-Methylmorpholine

(2.94 mL, 27.2 mmoles) was added over 5 min. The charging vessel was rinsed with DMSO (2.8 mL). HOBt/NMM solution (1.80 g, 2.66 mmoles, 20% w/w) was added in one portion. The charging vessel was rinsed with DMSO (2.8 mL). EDCI × HCl (7.16 g, 38.0 mmoles) was added over 10 min. at t_{jacket}= 22°C. The reaction was complete after 2 h. The reaction solution was then heated to 60°C and pH adjusted with TEA (5.18g g, 51.2 mmol) to pH~8. The solid mixture was cooled to 20°C after which H_2O (69.8mL) was added and left to stir for 16h. The product was filtered off, and slurry washed with cold H_2O (2 × 33 mL). Drying under vacuum at 40°C gave 7.53 g (22.8 mmoles, 99.0% w/w), 85% yield. ^{1}H-NMR (DMSO-d_6): δ 7.91 (br s, 1H), 7.78 (d, *J*=8.0 Hz, 2H), 7.29 (br s, 1H), 7.24 (d, *J*=8.0 Hz, 2H), 3.68-3.39 (m, 4H), 2.72-2.62 (m, 1H), 2.40-2.29 (m, 2H), 2.26-2.12 (m, 4H), 1.99-1.88 (m, 2H), 1.83-1.70 (m, 2H), 1.67-1.56 (m, 2H), 1.47-1.39 (m, 1H), 1.28-1.20 (m, 1H); LC-MS (ESI): *m/z* 328 (M+1). The chiral purity of the product was analyzed on a chiral column with UV-detection (250 nm) using isocratic method (mobile phase: Heptane/EtOH (80/20) + 0.1% Diethylamine) on Chiralpak AD-H, 4.6 x 150mm, giving an enantiomeric purity of >99% ee.

Second Method

4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide (10 gram, 30.54 mmoles) was dissolved in DMSO (83 ml) at 70°C and screened filtered into a reactor. The filter was rinsed with DMSO (17 ml) into the reactor. The temperature was decreased to 55°C and seed crystals of 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide were added (0.2 gram, 0.61 moles). Then after 30 minutes the slurry was cooled to 20°C over 3.5 hrs. At 20°C, water (40 ml) was charged over 2.5 hrs. After charging the slurry remained at 20°C for additional 12 hrs. before isolation. The solid product was washed (displacement wash) with a mixture of DMSO (28 ml) and water (12 ml) followed by three water (3x40 ml), one slurry wash and two displacement washes. Then the solid product was dried for 18 hrs. at 60°C. to obtain the title compound in 9.32 gram (28.5 mmoles), 93 % yield as crystals.

Third Method

4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide (3.0 gram, 9.16 mmoles) was dissolved in methanol (34.5 ml) and water (6.0 ml) at 65°C and

screened filtered into a reactor. Then the temperature was decreased to 55°C and followed by addition of seed crystals of 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide (0.06 gram, 0.18 mmoles). After 5 minutes the slurry was cooled to 20°C over 3.5 hrs. At 20°C, water (31.5 ml) was charged over 3.5 hrs. Then after additional 2 hrs, the solid form was isolated and washed twice with a mixture of methanol (9 ml) and water (3 ml). Finally, the solid product was dried at 60°C for 15 hrs to obtain the title compound in 2.49 gram. (7.60 mmoles), 81 % yield as crystals.

The solid product obtained in the first method was analysed by XRPD. A representative XRPD pattern is shown in Figure 1. Selected peaks are provided in Table 1. The XRPD pattern confirmed the solid material to be Crystalline Form I.

Table 1 Selected XRPD peaks of Crystalline Form I

Peak	Measured Angle [°2Th.]	Relative intensity
1	4.9	s
2	5.3	m
3	9.0	w
4	12.6	w
5	16.4	m
6	16.6	m
7	18.3	vs
8	19.6	s
9	20.4	s
10	21.2	m
11	23.2	m
12	24.6	w

The solid product obtained in the second and third method, respectively, were analysed by XRPD and a representative XRPD pattern as shown in Figure 1 and with selected peaks as

are provided in Table 1 were obtained. The XRPD pattern confirmed the solid material to be Crystalline Form I.

Solid product obtained according to method 1 of the Example 1 was analyzed by thermal techniques. DSC analysis indicated that Form I of Compound (I) is a high melting solid. The DSC-trace shows a small endothermic event, onset at 225°C, followed by a distinct endothermic event, onset at 235°C. A representative DSC thermogram is shown in Figure 2.

X-RAY POWDER DIFFRACTION ANALYSIS

An XRDP pattern for Crystalline Form I was collected using an XRPD instrumentation as described below.

An X-Ray Powder Diffraction (XRPD) pattern was collected under ambient conditions on a PANalytical X´Pert PRO MPD theta-theta system using long-fine-focus Cu Kα-radiation, wavelength of X-rays 1.5418 Å, at 45 kV and 40 mA . A programmable divergence slit and a programmable anti-scatter slit giving an irradiated length of 10 mm were used. 0.02 radian Soller slits were used on the incident and on the diffracted beam path. A 20 mm fixed mask was used on the incident beam path and a Nickel-filter was placed in front of a PIXcel-detector using 255 active channels. A thin flat sample was prepared on a flat zero background plate made of silicon using a spatula. The plate was mounted in a sample holder and rotated in a horizontal position during measurement. A diffraction pattern was collected between 2°2theta and 40°2theta in a continuous scan mode. Total time for the scan was approximately 10 minutes.

It is known in the art that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, persons skilled in the art of X-ray powder diffraction will realize that the relative intensities of peaks may vary according to the orientation of the sample under test and on the type and setting of the instrument used.

The skilled person will also realize that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute and any crystalline form that provides a power diffraction pattern substantially identical to those disclosed herein fall within the scope of the present disclosure (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996).

When herein reference is made to a compound according to the invention being crystalline, suitably the degree of crystallinity as determined by X-ray powder diffraction data, is for example greater than about 10%, is for example greater than about 20%, is for example greater than about 30%, is for example greater than about 40%, is for example greater than about 50%, is for example greater than about 60%, such as greater than about 80%, particularly greater than about 90%, more particularly greater than about 95%. In embodiments of the invention, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 98%, wherein the % crystallinity refers to the % by weight of the total sample mass which is crystalline.

Peak search on XRDP data of Crystalline Form I.

A manual peak search was done preceded by an angle correction against NIST SRM 676 alumina (α-Al_2O_3) standard.

The measured relative intensities vs. the strongest peak are given as very strong (vs) above 50%, as strong (s) between 25 and 50%, as medium (m) between 10 and 25% and as weak (w) between 5 and 10% relative peak height.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) ANALYSIS

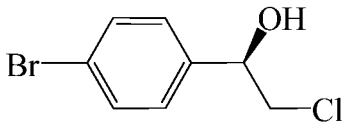
DSC from 25°C to 350°C was performed under nitrogen in an aluminum sample cup with a perforated lid using a NETZSCH DSC 204 instrument. The scan rate was 10°C per minute. The sample size was less than 1 mg. It is well known that the DSC onset and peak temperatures as well as energy values may vary due to, for example, the purity of the

sample and sample size and due to instrumental parameters, especially the temperature scan rate. Hence the DSC data presented are not to be taken as absolute values.
A person skilled in the art can set up instrumental parameters for a Differential scanning calorimeter so that data comparable to the data presented here can be collected according to standard methods, for example those described in Höhne, G. W. H. et al (1996), Differential Scanning Calorimetry, Springer, Berlin.

SYNTHESIS OF INTERMEDIATES

Intermediate A

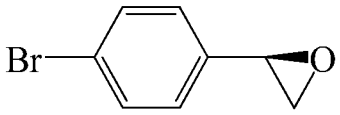
(*R*)-1-(4-Bromo-phenyl)-2-chloro-ethanol



Borane dimethylsulfide (2.0 kg, 24.8 moles, 94% w/w) was mixed in toluene (8 L) at t_{jacket}=20 °C. (*R*)-(+)-Methyl-CBS-oxazaborolidine (2.6 kg, 2.74 moles, 1M) as a toluene solution was added. The charging vessel was rinsed with toluene (0.5 L) and t_{jacket} was set to 45 °C. 1-(4-Bromo-phenyl)-2-chloro-ethanone (7.84 kg, 33.6 moles), which is commercially available from Jiangyan Keyan Fine Chemical Co. Ltd, was dissolved in 2-MeTHF (75 L) in a separate vessel and when t_{inner} was above 40 °C in the first vessel, the 2-MeTHF solution was added during 3 h. The latter vessel was rinsed with 2-MeTHF (2 L) and added to the reaction mixture, which was left stirring at t_{jacket}=45 °C for 1 h. At full conversion, the reaction mixture was cooled to t_{jacket}=10 °C before slow quench with MeOH (36 L). The first litre of MeOH was added during 30 min. and the rest during additional 30 min. MeOH was distilled off under vacuum at t_{jacket}=50 °C. The organic solution left was cooled to t_{jacket}=20 °C, washed with 1M HCl in H_2O (7 L conc HCl + 73 L H_2O) and concentrated under vacuum at t_{jacket}=50 °C to approximately 40 L. Intermediate A obtained in a 2-MeTHF solution can be stored at 10 °C for 20 h or used directly in the next synthetic step.

Intermediate B

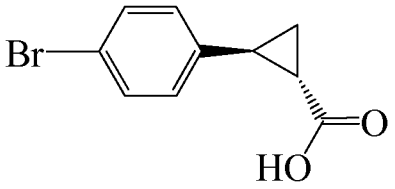
(*R*)-2-(4-Bromo-phenyl)-oxirane



Aliquat ® 175 (methyl tributyl ammonium chloride) (1.12 kg, 4.75 moles) was added to Intermediate A as a 2-MeTHF solution (33.6 moles, 40 L) at t_{jacket}=20 °C. NaOH (5.1 kg, 57.4 moles, 45% w/w) diluted in H_2O (2 L) was added during 20 min. The reaction mixture was left stirring at t_{jacket}=20 °C for 2 h. At full conversion the aq. phase was separated off and the organic phase washed with H_2O (2 × 25 L). 2-MeTHF (25 L) was added and the organic phase concentrated under vacuum at t_{jacket}=50 °C to approximately 30 L. Intermediate B obtained in a 2-MeTHF solution, can be stored at 5 °C for 140 h or used directly in the next synthetic step.

Intermediate C

(1*S*, 2*S*)-2-(4-Bromo-phenyl)-cyclopropanecarboxylic acid



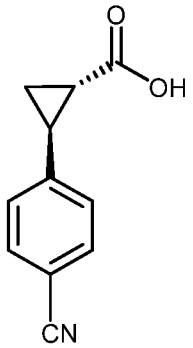
Triethyl phosphonoacetate (10.5 L, 51.9 moles, 98% w/w) was dissolved in 2-MeTHF (14 L) at t_{jacket}= −20 °C. Hexyl lithium in hexane (21 L, 48.3 moles, 2.3 M) was added at a rate to maintain t_{inner} below 0°C. The charging vessel was rinsed with 2-MeTHF (3 L) and the reaction solution was left stirring at t_{jacket}=10 °C. Intermediate B as a 2-MeTHF solution (33.6 moles, 30 L) was added during 20 min. The charging vessel was rinsed with 2-MeTHF (2 L) and the reaction solution was left stirring at t_{jacket}=65 °C for at least 16 h with the last 3 h at t_{jacket}=75 °C. At full conversion the reaction solution was cooled to t_{jacket}=20 °C. NaOH (7.6 kg, 85.5 moles, 45% w/w) diluted in H_2O (12 L) was added over 20 min. The reaction solution obtained was left stirring at t_{jacket}=60 °C for at least 2 h. At full conversion the reaction solution was cooled to t_{jacket}=20 °C, the aq. phase was separated off and the organic phase was extracted with H_2O (37 L). The combined aq. phases were

acidified to pH <3.5 with H_3PO_4 (9 L, 131 moles, 85% w/w) diluted in H_2O (12.5 L). Only 17 L of the diluted $H_3PO_{4\,(aq)}$ was used to achieve the pH <3.5. The acidic aq. phase was extracted with 2-MeTHF (2 × 15 L). The combined organic phases including rinsing with 2-MeTHF (2 L) were concentrated under vacuum at t_{jacket}=50 °C to approximately 11 L. The 2-MeTHF solution was diluted with EtOH (14.5 L) at t_{jacket}=35 °C and H_2O (16 L) was added over 20 min. The reaction solution was cooled to t_{jacket}=28 °C. Seed (16 g, 0.066 moles) was added and the solution was stirred for 2 h at t_{jacket}=28 °C. The reaction mixture was cooled to t_{jacket}=0 °C over 6 h and left stirring for at least 1 h. Additional H_2O (8 L) was added during 40 min. and the product was filtered off and washed with cold H_2O (10 L). Drying under vacuum at 40 °C gave 6.18 kg Intermediate C (21.5 moles, 84% w/w), 64% yield over four steps from 7.84 kg 1-(4-bromo-phenyl)-2-chloro-ethanone (33.6 moles).

Recrystallization of Intermediate C: Two batches of Intermediate C (6.18 + 7.04 kg) were mixed in EtOH (52 L) and heated at t_{jacket}=70 °C. H_2O (52 L) was added. The reaction solution was cooled to t_{jacket}=30 °C over 2.5 h. H_2O (16 L) was added during 20 min. and the crystallization was cooled to t_{jacket}=20 °C during 3 h. The product was filtered off and washed with a mixture of H_2O (8 L) and EtOH (2 L). Drying under vacuum at 40 °C gave 10.0 kg Intermediate (41.5 moles, 88% w/w), which was redissolved in toluene (39 L) and isooctane (57 L) at t_{jacket}=60 °C. A clear solution was obtained. The reaction solution was cooled to t_{jacket}=45 °C and left stirring for 1 h, then cooled to t_{jacket}=20 °C over 2 h. The product was filtered off and washed with a mixture of toluene (4 L) and isooctane (36 L) in two portions. Drying under vacuum at 40 °C gave 7.4 kg Intermediate C (29.8 moles, 97% w/w), 44% yield over four steps from 7.84 + 7.93 kg 1-(4-bromo-phenyl)-2-chloro-ethanone (67.5 moles). ^{1}H-NMR (DMSO-d_6): δ 12.36 (s, 1H), 7.44 (d, 2H, J=8 Hz), 7.13 (d, 2H, J=8 Hz), 2.39 (m, 1H), 1.81 (m, 1H), 1.43 (m, 1H), 1.33 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 173.76, 139.88, 131.20, 128.24, 119.14, 24.73, 24.31, 16.78; LC-MS (ESI): *m/z* 239 (M-1 (Br^{79})) and 241 (M-1 (Br^{81})).

Intermediate D

(1*S*, 2*S*)-2-(4-Cyano-phenyl)-cyclopropanecarboxylic acid

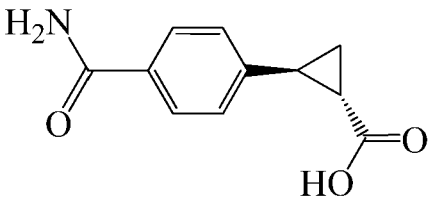


Intermediate C (3.7 kg, 14.9 moles, 97% w/w) and zinc-dust (98%+, <10μm) (99 g, 1.51 moles) were mixed with DMF (13.5 L) and the slurry was stirred at t_{jacket}=20 °C. The mixture was inerted and left with N_2 pressure of 0.1-0.2 bar. Bis(tri-*t*-butylphosphine)palladium (0) (27.5 g, 0.054 moles) was added to the slurry, and the vessel was inerted and left with N_2 pressure of 0.1-0.2 bar. The mixture was heated to t_{jacket}=45 °C, $Zn(CN)_2$ (1.0 kg, 8.52 moles) was added to the suspension in one portion, and the system was inerted and left with N_2 pressure of 0.1-0.2 bar (N.B. Cyanide salts are highly toxic). The resulting mixture was heated to t_{jacket}=75°C and stirred for at least 2 h. At full conversion the reaction mixture was cooled to t_{jacket}=20 °C. Thiol-functionalized silica (Silicycle, SiliaBond Thiol) (1.07 kg, 28% w/w) was added and the vessel was inerted. The reaction mixture was stirred for at least 36 h at t_{jacket}=20 °C. The scavenger was filtered off via a filter with activated charcoal or equivalent (pall-filter). The vessel and the filter system were washed with 2-MeTHF (53 L). The filtrate and washings were combined and stirred at t_{jacket}=5 °C. A pale yellow liquid resulted. NaCl (3.5 kg) in H_2O (16.4 L) was added during 15 min. at such a rate so the inner temperature remained below 15 °C. The resulting reaction mixture was heated to t_{jacket}=45 °C and the aq. phase was separated off. The organic phase was washed with $NaHSO_4 \times H_2O$ in H_2O (2 × (2.87 kg + 16.4 L)) and NaCl in H_2O (3.5 kg + 16.4 L). The organic phase was cooled to t_{jacket}=10 °C and NaOH (1.54 kg, 19.3 moles, 50% w/w) diluted in H_2O (41 L) was added during 45 min. The resulting reaction mixture was heated to t_{jacket}=30 °C and the organic phase separated off. The aq. phase was stirred at t_{jacket}=20 °C and pH adjusted to 6.5 with H_3PO_4 (0.90 kg, 7.81 moles, 85% w/w) diluted in H_2O (5.3 L) at a rate that maintained the inner temperature below 25 °C. 2-MeTHF and H_2O were distilled off under vacuum until a

volume 85-90% of the volume prior to distillation, approximately 8 L. The reaction mixture was cooled to t_{jacket}=0 °C and continued charging off H_3PO_4 (1.17 kg, 10.1 moles, 85% w/w) diluted in H_2O (8.2 L) until pH=4. The slurry was left stirring overnight at t_{jacket}=10 °C. The product was filtered off, washed with H_2O (2×4 L). Drying under vacuum at 40 °C gave Intermediate D (2.24 kg, 11.2 moles, 93.2% w/w), 75% yield. ^{1}H-NMR (DMSO-d_6): δ 12.45 (s, 1H), 7.72 (d, 2H, J=8 Hz), 7.37 (d, 2H, J=8 Hz), 2.50 (m, 1H), 1.94 (m, 1H), 1.50 (m, 1H), 1.42 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 173.51, 146.68, 132.27, 126.93, 118.97, 108.85, 25.16, 25.04, 17.44; LC-MS (ESI): *m/z* 186 (M-1).

Intermediate E

(1*S*, 2*S*)-2-(4-Carbamoyl-phenyl)-cyclopropanecarboxylic acid

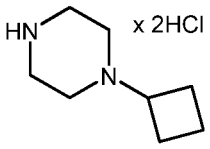


Intermediate D (4.46 kg, 22.0 moles, 92.5% w/w) was mixed in H_2O (40 L) at t_{jacket}=30 °C. NaOH (2.25 kg, 28.1 moles, 50% w/w) diluted in H_2O (6 L) was added at such a rate so t_{inner} remained below 35 °C. The charging vessel was rinsed with H_2O (1 L). If the pH was not ≥12, more NaOH was charged in the same concentration as previously. Hydrogen peroxide (4.89 kg, 50.3 moles, 35% w/w) was added at a rate to maintain t_{inner} below 35 °C. The charging vessel was rinsed with H_2O (1 L) and the reaction slurry was left stirring for 0.5−1.0 h. At full conversion the reaction mixture was cooled to t_{jacket}=0 °C and left stirring for at least 0.5 h when the temperature was reached. The sodium salt of Intermediate E was filtered off and washed with cold H_2O (2×7 L). The solid was slurry washed on the filter with $NaHSO_4 \times H_2O$ (2.76 kg, 20.0 moles) diluted in H_2O (35 L). The slurry was kept stirring at t_{jacket}=0 °C for 1 h. If the pH was not < 3.7, it was adjusted with $NaHSO_4 \times H_2O$ in H_2O. The product was filtered off, washed with cold H_2O (3 ×14 L). Drying under vacuum at 40 °C gave Intermediate E (4.0 kg, 18.2 moles, 93.4% w/w), 83% yield. ^{1}H-NMR (DMSO-d_6): δ 12.40 (s, 1H), 7.94 (s, 1H), 7.79 (d, 2H, J=8 Hz), 7.32 (s, 1H), 7.23 (d, 2H, J=8 Hz), 2.44 (m, 1H), 1.88 (m, 1H), 1.47 (m, 1H), 1.39 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 173.83, 167.67, 143.94, 132.17, 127.68, 125.73, 25.21, 24.67, 17.11; LC-MS (ESI): *m/z* 206 (M+1). The product was analyzed on a chiral column with UV-

detection using isocratic method (mobile phase: EtOH/Isohexane/TFA (15/85/0.1 v/v/v)) on Kromosil 3-Amycoat, 150 x 4.6 mm, 3 µm particle size, giving an enantiomeric purity of >99% ee, R_t=13.40 min (isomer 1) and 22.22 min (isomer 2).

Intermediate F

1-Cyclobutylpiperazine × 2HCl



N-Boc-piperazine (46 g, 0.25 moles), which is commercially available from SAFC, was dissolved in EtOH (415 mL) at t_{jacket}=20°C. Acetic acid (140 mL) was added in one portion followed by the addition of cyclobutanone (26.5 g, 0.37 moles). The charging vessel was rinsed with EtOH (25 mL) and the light yellow solution was left stirring at t_{jacket}=20°C for 1 h. $NaBH(OAc)_3$ (80 g, 0.36 moles, 95% w/w) was added in 20 portions over 2 h. EtOH (25 mL) was used for rinsing. The reaction mixture was left stirring for 2 h. At full conversion NAOH (296 g, 3.70 moles, 50% w/w) diluted in H_2O (230 mL) was added at such a rate so t_{inner} remained below 35°C.

EtOH was distilled off under vacuum at t_{jacket}=45°C to approximately 650 mL. The water phase was extracted with toluene (550 mL) at t_{jacket}=45°C and the obtained organic phase was concentrated under vacuum at t_{jacket}=45°C to approximately 250 mL. The toluene solution was diluted with 2-propanol (140 mL) at t_{jacket}=20°C and H_2O (2.2 mL, 0.12 moles) was added. HCl in 2-propanol (82 mL, 0.49 moles, 6M) diluted in 2-propanol (140 mL) was added over 30 min at t_{jacket}=20°C. The reaction solution was heated to t_{jacket}=48°C. HCl in 2-propanol (164 mL, 0.99 moles, 6M) diluted in 2-propanol (276 mL) was added over 2 h at t_{inner}=46°C. The reaction solution was kept at t_{jacket}=48°C for an additional 4 h before cooling to t_{jacket}=10°C over 1 h. The product was filtered off and washed with cold 2-propanol (2 × 230 mL). Drying under vacuum at 40°C gave 44 g Intermediate F (0.20 moles, 95.9% w/w), 80 % yield. ^{1}H-NMR (DMSO-d_6): δ 12.46 (s, 1H), 10.07 (s, 2H), 3.73 (m, 1H), 3.05-3.61 (m, 8 H), 2.37 (m, 2H), 2.14 (m, 2H), 1.70 (m, 2H); ^{13}C-NMR (DMSO-d_6): δ 58.05, 44.67, 39.59, 24.38, 13.18.

GENERAL METHODS

^{1}H NMR spectra were recorded in the indicated deuterated solvent at 400 MHzor 500MHz. The 400MHz spectra were obtained using a Bruker av400 NMR spectrometer equipped with a 3mm flow injection SEI ^{1}H/D-^{13}C probe head with Z-gradients, using a BEST 215 liquid handler for sample injection, or using a Bruker DPX400 NMR or Bruker 500MHz ultrashield spectrometer equipped with a 4-nucleus probehead with Z-gradients. Chemical shifts are given in ppm down- and upfield from TMS. Resonance multiplicities are denoted s, d, t, q, m and br for singlet, doublet, triplet, quartet, multiplet, and broad respectively.

Mass spectra (MS) were run using an automated system with electrospray (+ESI) ionization. Generally, only spectra where parent masses are observed are reported. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine or bromine is present).

LC-MS analyses were recorded on a Waters LCMS equipped with a Waters X-Terra MS, C8-column, (3.5 µm, 100 mm x 3.0 mm i.d.). The mobile phase system consisted of A: 10 mM ammonium acetate in water/acetonitrile (95:5) and B: acetonitrile. A linear gradient was applied running from 0% to 100% B in 4-5 minutes with a flow rate of 1.0 mL/min. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The capillary voltage was 3 kV and the mass spectrometer was typically scanned between *m/z* 100-700. Alternative, LC-MS HPLC conditions were as follows: Column: Agilent Zorbax SB-C8 (5 µm, 50mm x 2mm i.d) Flow: 1.0 mL/minGradient: 95% A to 100% B in 5 min. A = 5% acetonitrile in water with 0.1% formic acid and B = acetonitrile with 0.1% formic acid,UV-DAD 210-400 nm. Alternative, LC-MS analyses were recorded on a Waters 2790 LCMS equipped with a Phenomenex Luna C18 (5 µm, 50x 4.6mm i.d.) The mobile phase system consisted of A: 10 mM ammonium formate (pH 4) in water and B: acetonitrile. A linear gradient was applied running from 95% to 5% B in 5 minutes with a flow rate of 2.0 mL/min. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The capillary voltage was 3 kV and the mass spectrometer was typically scanned between *m/z* 100-700. . Alternative, LC-MS analyses were recorded on a

Agilent 1200 LCMS equipped with a Zorbax SB C8 (3.5µm, 150x 4.6mm i.d.) The mobile phase system consisted of A: 0.05%TFA in water and B: acetonitrile. A linear gradient was applied running from 10% to 90% B in 8 minutes with a flow rate of 1.0 mL/min. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The capillary voltage was 3 kV and the mass spectrometer was typically scanned between *m/z* 100-700.

The compounds have been named using CambridgeSoft MedChem ELN v2.1, ACD/Name, version 8.08, software from Advanced Chemistry Development, Inc. (ACD/

ABBREVIATION LIST

ACN: acetonitrile; aq: aqueous; br: broad; Bu: butyl; calcd: calculated; Celite®: brand of diatomaceous earth filtering agent, registered trader of Celite Corporation; d: doublet; dd: doublet of doublet; ddd: doublet of doublet of doublet; dddd: doublet of doublet of doublet of doublet; DMF: *N,N*-dimethyl formamide; DMSO: dimethyl sulfoxide; dq: doublet of quartet; DSC: differential scanning calorimetry; dt: doublet of triplet; DVS: dynamic vapour sorption; EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; ESI: electrospray ionization; EtOAc: ethyl acetate; EtOH: ethanol; Et: ethyl; FT-IR: Fourier-transform infrared; FT-Raman: Fourier transform Raman; g: gram; h: hour(s); ^{1}H NMR: proton nuclear magnetic resonance; HOBT: N-Hydroxybenzotriazole; HPLC: high pressure liquid chromatography; iPrOH: iso-propanol; L: liter; m: multiplet; M: molar; mL: milliliter; Me: methyl; MeOH: methanol; mg: milligram; 2-MeTHF: 2-methyl tetrahydrofuran; MHz: megahertz; min: minute(s); mmol: millimole; mol: mole; MS: mass spectrometry; MTBE: methyl *tert*-butyl ether; $NaHCO_3$: sodium bicarbonate; Pd/C: palladium on carbon; ppm: parts per million; q: quartet; quin: quintet; rt: room temperature; s: singlet; sat: saturated; t: triplet;TEA: triethylamine; tBuOH: *tert*-butanol; td: triplet of doublet; TFA: trifluoroacetic acid; TGA = thermalgravimetric analysis; THF: tetrahydrofuran; UV = ultraviolet; XRPD = X-ray powder diffraction; and the prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and tertiary.

PHARMACOLOGY

Human histamine H3 binding assay with the Agonist Radioligand [^{3}H]-N-a-methylhistamine

The H3 binding assay was used to evaluate the ability of a compound of formula (I) to inhibit [^{3}H]-N-a-methylhistamine under the conditions as described below:
All binding assays were performed in a buffer consisting of 20 mmol/L Hepes, 100 mmol/L NaCl. The pH was set at 7.4 at room temperature. Liquid handling robots were used to prepare, in drug plates, 10 points dose response curves of the compound of formula (I) (3-fold serial dilutions, starting at 10 μmol/L). The assay, performed in 96-well plates, consisted of 100 μL, containing 20 μL of buffer alone for total binding (column #1), 20 μL of imetit (5X) for the non specific binding (column #2), 20 μL of the compound of formula (I) (5X) at varying concentrations (column #3 to #12), plus 20 μL of [3H]-N-α-Methylhistamine (25 000 dpm/well, 1.5 nmol/L) in all wells and finally 60 μL of membranes (20 μg of protein/well) mix is added to start the reaction. Membranes and SPA beads (1000 μg/well) were mixed together and incubated for 30 minutes at room temperature prior to the start of the assay. Eight wells (column #1) were used to define total binding and 1 μmol/L imetit (eight wells, column #2) define the non-specific binding. Plates were then mixed on an orbital mixer, incubated 90 minutes at room temperature, and then read on a Trilux 384™ counter.

Guanosine 5'-*O*-(3-[^{35}S]thio)triphosphate [GTPgS] Binding Assay

[^{35}S]GTPγS binding assay was performed in a buffer consisting of 20 mmol/L Hepes, 100 mmol/L NaCl, 10 mmol/L $MgCl_2$, 3 μg/mL saponine and 10 μmol/L GDP. The pH was set at 7.4 at room temperature. Liquid handling robots were used to prepare, in drug plates, 10 points dose response curves of the compound of formula (I) (3-fold serial dilutions, starting at 1 μmol/L for hH3 receptors and 10 μmol/L for rH3 receptors). The assay, performed in 96-well plates, consisted of 120 μL, containing 20 μL of RαMH (EC80, antagonist mode), 20 μL the compound of formula (I) at varying concentrations, 20 μL of the tracer [35S]GTPγS (60000 dpm/well, 0.2 nmol/L) and finally 60 μL of membranes (10 μg of protein/well for hH3) mix is added to start the reaction. Membranes, SPA beads (125 μg/well) and GDP were mixed together and incubated for 30 minutes at room temperature

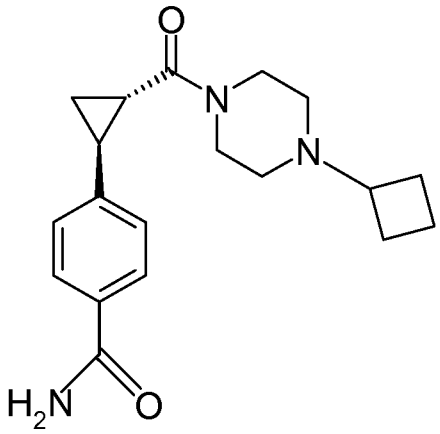
prior to the start of the assay. Eight wells were used to define baseline and RαMH EC_{80} (30 nmol/L for hH3 receptors) define the positive control. Plates were then mixed (2 minutes) on an orbital mixer, incubated 60 minutes at room temperature, and then read on a Trilux 384™ counter.

RESULTS

A compound formula (I) showing pIC_{50} values that were generated in accordance with the assays described above, the inhibit specific binding of [^{3}H]-N-α-Methyl Histamine to the human H3 receptor (445 aa)) as 7.9 ±0.060 (13 nmol/L) and the inhibition of H3 agonist R-α-Methyl-Histamine stimulated-[^{35}S]GTPγS binding as 8.5 ±0.14 (3.0 nmol/L).

CLAIMS

1. A crystalline form of compound (I), 4-{(1S, 2S)-2-[(4-cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide,



(I).

2. A crystalline form of compound (I) of claim 1, characterized in that said form has an XRPD pattern (Cu Kα) with at least one peak at about 18.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

3. A crystalline form of compound (I) of claim 1, characterized in that said form has an XRPD pattern (Cu Kα) with at least two peaks at about 4.9 and about 18.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

4. A crystalline form of compound (I) of claim 1, characterized in that said form has an XRPD pattern (Cu Kα) with at least three peaks at about 4.9, about 18.3 and about 20.4 °2Theta when measured using radiation with a wavelength of about 1.54 angstroms.

5. A crystalline form of compound (I) of claim 1, characterized in that said form has an XRPD pattern (Cu Kα) with at least four peaks at about 4.9, about 18.3 about 19.6 and 20.4 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

6. A crystalline form of compound (I) of any one of claims 3-5, wherein the XRPD pattern (Cu Kα) further comprises peaks at about 16, 4 and about 16.6, about 18.3 and about 19.6 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

7. A crystalline form of compound (I) of any one of claims 3-6, wherein the XRPD pattern (Cu Kα) further comprises a peak at about 5.3 °2Theta, when measured using radiation with a wavelength of about 1.54 angstroms.

8. A crystalline form of compound (I) of claim 1, characterized in that said form has an XRPD pattern (Cu Kα) with peaks at about 4.9, about 5.3, about 9.0, about 12.6, about 16.4, about 16.6, about 18.3, about 19.6, about 20.4, about 21.2, about 23.2 and about 24.6 °2Theta when measured using radiation with a wavelength of about 1.54 angstroms.

9. A crystalline form of compound (I) of claim 1, characterized by the XRPD pattern essentially as shown in Figure 1.

10. A crystalline form of compound (I) of any one of claims 3-9, characterized by the DSC thermogram comprising an endotherm at about 235°C.

11. A crystalline form of compound (I) of claim 10, characterized by the DSC thermogram comprising an additional small endotherm at about 225°C.

12. A crystalline form of compound (I) of any one of claims 3-9, characterized by the DSC thermogram essentially as shown in Figure 2.

13. A crystalline form of compound (I) of any one of claims 1-12, which is substantially pure.

14. A pharmaceutical formulation comprising a crystalline form of compound (I) as claimed in any one of claims 1-13 in association with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

15. A crystalline form of compound (I) according to any one of claims 1-13 for use in therapy.

16. A crystalline form of compound (I) according to any one of claims 1-13 for use in the manufacture of a medicament for the treatment of a disorder selected from schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, Alzheimer's disease, cognition deficiency, and cognition deficiency associated with schizophrenia.

17. A crystalline form of compound (I) according to any one of claims 1-13 for use in the treatment of schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, Alzheimer's disease, cognition deficiency, and cognition deficiency associated with schizophrenia.

18. A method for the therapy of a disorder selected from schizophrenia, narcolepsy, excessive daytime sleepiness, obesity, attention deficit hyperactivity disorder, pain, neuropathic pain, Alzheimer's disease, cognition deficiency, and cognition deficiency associated with schizophrenia, in a warm-blooded animal, comprising administering to said animal in need of such therapy a therapeutically effective amount of a crystalline form of compound (I) according to any one of claims 1-13.