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(54) **Title**: CRYSTALLINE FORM OF (S)-(2-(6-CHLORO-7-METHYL-1H-BENZO[D]IMIDAZOL-2-YL)-2-METHYLPYRROLIDIN-1 -YL)(5-METHOXY-2-(2H-1,2,3-TRIAZOL-2-YL)PHENYL)METHANONE AND ITS USE AS OREXIN RECEPTOR ANTAGONISTS

(57) **Abstract**: The invention relates to crystalline forms of (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2- yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone, processes for the preparation thereof, pharmaceutical compositions containing such crystalline forms, pharmaceutical compositions prepared from such crystalline forms, and their use as a medicament, especially as orexin receptor antagonists.

CRYSTALLINE FORM OF (S)-(2-(6-CHLORO-7-METHYL-1H-BENZO[D]IMIDAZOL-2-YL)-2-METHYLPYRROLIDIN-1 -YL)(5-METHOXY-2-(2H-1 ,2,3-TRIAZOL-2-YL)PHENYL)METHANONE AND ITS USE AS OREXIN RECEPTOR ANTAGONISTS

The invention relates to a novel crystalline forms of (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone (hereinafter also referred to as "COMPOUND"), processes for the preparation thereof, pharmaceutical compositions comprising said crystalline forms, pharmaceutical compositions prepared from such crystalline forms, and their use as orexin receptor antagonists in the treatment or prevention of sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders.

Orexins (orexin A or OX-A and orexin B or OX-B) are neuropeptides found in 1998 by two research groups, orexin A is a 33 amino acid peptide and orexin B is a 28 amino acid peptide (Sakurai T. *et al.*, Cell, **1998**, 92, 573-585). Orexins are produced in discrete neurons of the lateral hypothalamus and bind to the G-protein-coupled receptors (OX_1 and OX_2 receptors). The orexin-1 receptor (OX_1) is selective for OX-A, and the orexin-2 receptor (OX_2) is capable to bind OX-A as well as OX-B. Orexin receptor antagonists are a novel type of nervous system or psychotropic drugs. Their mode of action in animals and humans involves either blockade of both orexin-1 and orexin-2 receptor (dual antagonists), or individual and selective blockade of either the orexin-1 or the orexin-2 receptor (selective antagonists) in the brain. Orexins were initially found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behaviour (Sakurai T. *et al.*, Cell, **1998**, 92, 573-585).

On the other hand, orexin neuropeptides and orexin receptors play an essential and central role in regulating circadian vigilance states. In the brain, orexin neurons collect sensory input about internal and external states and send short intrahypothalamic axonal projections as well as long projections to many other brain regions. The particular distribution of orexin fibers and receptors in basal forebrain, limbic structures and brainstem regions - areas related to the regulation of waking, sleep and emotional reactivity- suggests that orexins exert essential functions as regulators of behavioral arousal; by activating wake-promoting cell firing, orexins contribute to orchestrate all brain arousal systems that regulate circadian activity, energy balance and emotional reactivity. This role opens large therapeutic opportunities for medically addressing numerous mental health disorders possibly relating to orexinergic dysfunctions [see for example: Tsujino N and Sakurai T, "Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward systems.", Pharmacol Rev. **2009**, 61:162-176; and Carter ME et al., "The brain hypocretins and their receptors: mediators of allostatic arousal.", Curr Op Pharmacol. **2009**, 9: 39-45] that are

described in the following sections. It was also observed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches to insomnia and other sleep disorders (Chemelli R.M. *et al.*, Cell, **1999**, 98, 437-451).

Human memory is comprised of multiple systems that have different operating principles and different underlying neuronal substrates. The major distinction is between the capacity for conscious, declarative memory and a set of unconscious, non-declarative memory abilities. Declarative memory is further subdivided into semantic and episodic memory. Non-declariative memory is further subdivided into priming and perceptual learning, procedural memory for skills and habits, associative and non-associative learning, and some others. While semantic memory refers to the general knowledge about the world, episodic memory is autobiographical memory of events. Procedural memories refer to the ability to perform skill-based operations, as e.g. motor skills. Long-term memory is established during a multiple stage process through gradual changes involving diverse brain structures, beginning with learning, or memory acquisition, or formation. Subsequently, consolidation of what has been learned may stabilize memories. When long-term memories are retrieved, they may return to a labile state in which original content may be updated, modulated or disrupted. Subsequently, reconsolidation may again stabilize memories. At a late stage, long-term memory may be resistant to disruption. Long-term memory is conceptually and anatomically different from working memory, the latter of which is the capacity to maintain temporarily a limited amount of information in mind. Behavioural research has suggested that the human brain consolidates long-term memory at certain key time intervals. The initial phase of memory consolidation may occur in the first few minutes after we are exposed to a new idea or learning experience. The next, and possibly most important phase, may occur over a longer period of time, such as during sleep; in fact, certain consolidation processes have been suggested to be sleep-dependent [R. Stickgold et al., Sleep-dependent memory consolidation; Nature **2005**,437, 1272-1278]. Learning and memory processes are believed to be fundamentally affected in a variety of neurological and mental disorders, such as e.g. mental retardation, Alzheimer's disease or depression. Indeed, memory loss or impairment of memory acquisition is a significant feature of such diseases, and no effective therapy to prevent this detrimental process has emerged yet.

In addition, both anatomical and functional evidence from in vitro and in vivo studies suggest an important positive interaction of the endogenous orexin system with reward pathways of the brain [Aston-Jones G et al., Brain Res **2010**, 1314, 74-90; Sharf R et al., Brain Res **2010**, 1314, 130-138]. Selective pharmacological OXR-1 blockade reduced cue- and stress-induced reinstatement of cocaine seeking [Boutrel B, et al., "Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior." Proc Natl Acad Sci **2005**,

102(52), 19168-19173; Smith RJ et al., "Orexin/hypocretin signaling at the orexin 1 receptor regulates cue-elicited cocaine-seeking." Eur J Neurosci **2009**, 30(3), 493-503; Smith RJ et al., "Orexin/hypocretin is necessary for context-driven cocaine-seeking." Neuropharmacology 2010, 58(1), 179-184], cue-induced reinstatement of alcohol seeking [Lawrence AJ et al., Br J Pharmacol **2006**, 148(6), 752-759] and nicotine self-administration [Hollander JA et al., Proc Natl Acad Sci **2008**, 105(49), 19480-19485; LeSage MG et al., Psychopharmacology **2010**, 209(2), 203-212]. Orexin-1 receptor antagonism also attenuated the expression of amphetamine- and cocaine-induced CPP [Gozzi A et al., PLoS One **2011**, 6(1), e16406; Hutcheson DM et al., Behav Pharmacol **2011**, 22(2), 173-181], and reduced the expression or development of locomotor sensitization to amphetamine and cocaine [Borgland SL et al., Neuron **2006**, 49(4), 589-601; Quarta D et al., "The orexin-1 receptor antagonist SB-334867 reduces amphetamine-evoked dopamine outflow in the shell of the nucleus accumbens and decreases the expression of amphetamine sensitization." Neurochem Int **2010**, 56(1), 11-15].

The effect of a drug to diminish addictions may be modelled in normal or particularly sensitive mammals used as animal models [see for example Spealman et al, Pharmacol. Biochem. Behav. **1999**, *64*, 327-336; or T.S. Shippenberg, G.F. Koob, "Recent advances in animal models of drug addiction" in Neuropsychopharmacology: The fifth generation of progress; K.L.Davis, D. Charney, J.T.Doyle, C. Nemeroff (eds.) **2002**; chapter 97, pages 1381-1397].

Several converging lines of evidence furthermore demonstrate a direct role of the orexin system as modulator of the acute stress response. For instance, stress (i.e. psychological stress or physical stress) is associated with increased arousal and vigilance which in turn is controlled by orexins [Sutcliffe, JG et al., Nat Rev Neurosci **2002**, 3(5), 339-349]. Orexin neurons are likely to be involved in the coordinated regulation of behavioral and physiological responses in stressful environments [Y. Kayaba et al., Am. J. Physiol. Regul. Integr. Comp. Physiol. **2003,** 285:R581-593]. Hypocretin/orexin contributes to the expression of some but not all forms of stress and arousal [Furlong T M et al., Eur J Neurosci **2009**, 30(8), 1603-1614]. Stress response may lead to dramatic, usually time-limited physiological, psychological and behavioural changes that may affect appetite, metabolism and feeding behavior [Chrousos, GP et al., *JAMA* **1992**, 267(9), 1244-1252]. The acute stress response may include behavioural, autonomic and endocrinological changes, such as promoting heightened vigilance, decreased libido, increased heart rate and blood pressure, or a redirection of blood flow to fuel the muscles, heart and the brain [Majzoub, JA et al., European Journal of Endocrinology **2006**, 155 (suppl_1) S71-S76].

As outlined above the orexin system regulates homeostatic functions such as sleep-wake cycle, energy balance, emotions and reward. Orexins are also involved in mediating the acute behavioral and autonomous nervous system response to stress [Zhang Wet al., "Multiple components of the defense response depend on orexin: evidence from orexin knockout mice and orexin neuron-ablated mice." Auton Neurosci **2006**, 126-127, 139-145]. Mood disorders including all types of depression and bipolar disorder are characterized by disturbed “mood” and feelings, as well as by sleeping problems (insomnia as well as hypersomnia), changes in appetite or weight and reduced pleasure and loss of interest in daily or once enjoyed activities [Liu X et al., Sleep **2007**, 30(1): 83-90]. Thus, there is a strong rationale that disturbances in the orexin system may contribute to the symptoms of mood disorders. Evidence in humans, for instance, exists that depressed patients show blunted diurnal variation in CSF orexin levels [Salomon RM et al., Biol Psychiatry **2003**, 54(2), 96-104]. In rodent models of depression, orexins were also shown to be involved. Pharmacological induction of a depressive behavioral state in rats, for instance, revealed an association with increased hypothalamic orexin levels [Feng P et al., J Psychopharmacol **2008**, 22(7): 784-791]. A chronic stress model of depression in mice also demonstrated an association of molecular orexin system disturbances with depressed behavioral states and a reversal of these molecular changes by antidepressant treatment [Nollet et al., NeuroPharm **2011**, 61(1-2):336-46].

The orexin system is also involved in stress-related appetitive/reward seeking behaviour (Berridge CW et al., Brain Res **2009**, 1314, 91-102). In certain instances, a modulatory effect on stress may be complementary to an effect on appetitive/reward seeking behaviour as such. For instance, an OX_1 selective orexin receptor antagonist was able to prevent footshock stress induced reinstatement of cocaine seeking behaviour [Boutrel, B et al., Proc Natl Acad Sci **2005**, 102(52), 19168-19173]. In addition, stress is also known to play an integral part in withdrawal which occurs during cessation of drug taking (Koob, GF et al., Curr Opin Investig Drugs **2010**, 11(1), 63-71).

Orexins have been found to increase food intake and appetite [Tsujino, N, Sakurai, T, Pharmacol Rev **2009**, 61(2) 162-176]. As an additional environmental factor, stress can contribute to binge eating behaviour, and lead to obesity [Adam, TC et al. Physiol Be*hav* **2007**, 91(4) 449-458]. Animal models that are clinically relevant models of binge eating in humans are described for example in W. Foulds Mathes et al.; Appetite **2009**, 52, 545–553.

A number of recent studies report that orexins may play a role into several other important functions relating to arousal, especially when an organism must respond to unexpected stressors and challenges in the environment [Tsujino N and Sakurai T. Pharmacol Rev.

2009, 61:162-176; Carter ME, Borg JS and deLecea L., Curr Op Pharmacol. **2009**, 9: 39-45; C Boss, C Brisbare-Roch, F Jenck, Journal of Medicinal Chemistry **2009**, 52: 891-903]. The orexin system interacts with neural networks that regulate emotion, reward and energy homeostasis to maintain proper vigilance states. Dysfunctions in its function may thus relate to many mental health disorders in which vigilance, arousal, wakefulness or attention is disturbed.

The compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide (WO2005/118548), a dual orexin receptor antagonist, showed clinical efficacy in humans when tested for the indication primary insomnia. In the rat, the compound has been shown to decrease alertness, characterized by decreases in both active wake and locomotion; and to dose-dependently increase the time spent in both REM and NREM sleep [Brisbare et al., Nature Medicine **2007**, *13*, 150-155]. The compound further attenuated cardiovascular responses to conditioned fear and novelty exposure in rats [Furlong T M et al., Eur J Neurosci **2009**, 30(8), 1603-1614]. It is also active in an animal model of conditioned fear: the rat fear-potentiated startle paradigm (WO2009/047723) which relates to emotional states of fear and anxiety diseases such as anxieties including phobias and post traumatic stress disorders (PTSDs). In addition, intact declarative and non-declarative learning and memory has been demonstrated in rats treated with this compound [WO2007/105177, H Dietrich, F Jenck, Psychopharmacology **2010**, 212, 145-154]. Said compound furthermore decreased brain levels of amyloid-beta (Aβ) as well as Aβ plaque deposition after acute sleep restriction in amyloid precursor protein transgenic mice [JE Kang et al., "Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle.", Science **2009**, 326(5955): 1005-1007]. The accumulation of the Aβ in the brain extracellular space is hypothesized to be a critical event in the pathogenesis of Alzheimer's disease. The so-called and generally known "amyloid cascade hypothesis" links Aβ to Alzheimer's disease and, thus, to the cognitive dysfunction, expressed as impairment of learning and memory. The compound has also been shown to induce antidepressant-like activity in a mouse model of depression, when administered chronically [Nollet et al., NeuroPharm **2011**, 61(1-2):336-46]. Moreover, the compound has been shown to attenuate the natural activation induced by orexin A in fasted hungry rats exposed to food odors [MJ Prud'homme et al., Neuroscience **2009**, 162(4), 1287-1298]. The compound also displayed pharmacological activity in a rat model of nicotine self-administration [LeSage MG et al., Psychopharmacology **2010**, 209(2), 203-212]. Another dual orexin receptor antagonist, N-biphenyl-2-yl-1-{[(1-methyl-1H-benzimidazol-2-yl)sulfanyl]acetyl}-L-prolinamide inhibited nicotine-reinstatement for a conditioned reinforcer and reduced behavioral (locomotor sensitization) and molecular (transcriptional responses) changes induced by repeated

amphetamine administration in rodents [Winrow et al., Neuropharmacology **2009**, 58(1),185-94].

Orexin receptor antagonists comprising a 2-substituted saturated cyclic amide derivatives (such as 2-substituted pyrrolidine-1-carboxamides) are known for example from WO2008/020405, WO2008/038251, WO2008/081399, WO2008/087611, WO2008/117241, WO2008/139416, WO2009/004584, WO2009/016560, WO2009/016564, WO2009/040730, WO2009/104155, WO2010/004507, WO2010/038200, WO2001/096302, WO2002/044172, WO2002/089800, WO2002/090355, WO2003/002559, WO2003/032991, WO2003/041711, WO2003/051368, WO2003/051873, WO2004/026866, WO2004/041791, WO2004/041807, WO2004/041816, WO2009/003993, WO2009/003997, WO2009/124956, WO2010/060470, WO2010/060471, WO2010/060472, WO2010/063662, WO2010/063663, WO2010/072722, WO2010/122151, and WO2008/150364. A particular pyrrolidine derived compound is disclosed in Langmead et. al, Brit. J. Pharmacol. **2004**, 141, 340-346 as being highly orexin-1 selective. WO2003/002561 discloses certain N-aroyl cyclic amine derivatives, encompassing benzimidazol-2-yl-methyl substituted pyrrolidine derivatives, as orexin receptor antagonists. Despite the great number of prior art compounds and their high structural variability, all compounds share a common structural feature, i.e. in position 2 of the saturated cyclic amide a linker group such as at least a methylene group (or longer groups such as $-CH_2-NH-CO-$, $-CH_2-NH-$, $-CH_2-O-$, $-CH_2-S-$, etc.) link the cyclic amide to the respective aromatic ring system substituent. Despite the substantial conformational changes that may be expected from the removal of a linker between two rigid structural elements, the compound of the present crystalline forms, that has a benzimidazole ring directly attached to a pyrrolidine amide in position 2, is a dual antagonist of the orexin 1 receptor and of the orexin 2 receptor and, thus, is of potential use in the treatment of disorders relating to orexinergic dysfunctions, comprising especially sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders; and especially in the treatment of sleep disorders, anxiety disorders, and addiction disorders.

It has now been found that certain crystalline forms of COMPOUND may under certain conditions be found. Said crystalline forms of COMPOUND are novel and may have advantageous properties in view of the potential use of COMPOUND as active pharmaceutical ingeredient. Such advantages may include better flow properties; less hygroscopicity; better reproducibiliy in manufacturing (for example better filtration parameters, better reproducibility of formation, and/or better sedimentation); and/or defined morphology. Such crystalline forms of COMPOUND may be particularly suitable in a process of manufacturing certain pharmaceutical compositions, especially lipid-based pharmaceutical compositions.

Description of the Figures

Figure 1 shows the X-ray powder diffraction diagram of COMPOUND in amorphous form as obtained from Reference Example 1. The X-ray diffraction diagram shows amorphous material.

Figure 2 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form 1 as obtained from Example 1. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensitites given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-40° 2theta with relative intensity larger then 10% are reported): 8.6° (84%), 11.5° (45%), 13.4° (44%), 14.6° (43%), 15.2° (100%), 15.5° (72%), 17.1° (36%), 18.4° (22%), 19.3° (42%), 19.8° (27%), 21.3° (62%), 21.9° (14%), 22.4° (36%), 23.1° (13%), 23.5° (25%), 25.7° (27%), 26.4° (36%), 26.8° (22%), 27.9° (22%), and 29.7° (17%)

Figure 3 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form 2 as obtained from Example 2. The X-ray diffraction diagram measured with method 2 shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensitites given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-40° 2theta with relative intensity larger then 10% are reported): 7.2° (38%), 10.9° (69%), 13.4° (83%), 14.3° (70%), 14.5° (70%), 14.9° (71%), 16.1° (14%), 17.2° (47%), 18.3° (82%), 19.8° (14%), 20.0° (11%), 20.6° (15%), 20.9° (85%), 21.1° (100%), 21.8° (44%), 22.3° (14%), 22.9° (27%), 24.0° (71%), 27.7° (13%), 25.0° (17%), 25.2° (30%), 27.0° (16%), 27.3° (32%), 28.9° (13%), 30.1° (45%), 30.4° (13%), 32.7° (11%), and 36.0° (16%)

For avoidance of any doubt, the above-listed peaks describe the experimental results of the X-ray powder diffraction shown in Figure 2, respectively Figure 3. It is understood that, in contrast to the above peak list, only a selection of characteristic peaks is required to fully and unambiguously characterize of the COMPOUND in the respective crystalline form of the present invention.

In the X-ray diffraction diagrams of Fig. 1 to Fig 3 the angle of refraction 2theta (2θ) is plotted on the horizontal axis and the counts on the vertical axis.

Figure 4 shows the gravimetric vapour sorption diagram of COMPOUND in amorphous free base form as obtained from Reference Example 1.

Figure 5 shows the gravimetric vapour sorption diagram of COMPOUND in a crystalline form 1 as obtained from Example 1.

Figure 6 shows the gravimetric vapour sorption diagram of COMPOUND in a crystalline form 2 as obtained from Example 2.

In the gravimetric vapour sorption diagrams of Figure 4 to Figure 6 the relative humidity (% RH) is plotted on the horizontal axis and the mass change (% dm) on the vertical axis.

Detailed Description of the Invention

1) A first embodiment of the invention relates to crystalline forms of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone; characterized by:

a. the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3°; or
b. the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0°.

It is understood, that the crystalline forms according to embodiment 1) comprise COMPOUND in a crystalline form of the free base (i.e. not in form of a salt). Furthermore, said crystalline forms may comprise non-coordinated and / or coordinated solvent. Coordinated solvent is used herein as term for a crystalline solvate. Likewise, non-coordinated solvent is used herein as term for physiosorbed or physically entrapped solvent (definitions according to Polymorphism in the Pharmaceutical Industry (Ed. R. Hilfiker, VCH, 2006), Chapter 8: U.J. Griesser: The Importance of Solvates). Crystalline form 1 in particular is a hemihydrate, i.e. it comprises about 0.5 equivalents of coordinated water, and may comprise additional non-coordinated solvent such as isopropanol, ethanol and / or water, especially water. Cystalline form 2 in particular comprises no coordinated water, but may comprise non-coordinated solvent such as isopropanol, ethanol and / or water.

2) Another embodiment relates to a crystalline form of COMPOUND according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3°.

3) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3° according to embodiment 1); or to such crystalline form according to embodiment 2), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 11.5°, 13.4°, 14.6°, 15.2°, 15.5°, 19.3°, 21.3°, 22.4°, and 26.4°.

4) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of

refraction 2θ: 8.6°, 15.2°, and 21.3° according to embodiment 1); or to such crystalline form according to embodiment 2) or 3), which essentially shows the X-ray powder diffraction pattern as depicted in Figure 2.

5) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3° according to embodiment 1); or to such crystalline form according to any one of embodiments 2) to 4), which has a broad endothermal event in the range of about 50 to 160°C as determined by differential scanning calorimetry using the method as described herein.

6) In another embodiment the present invention relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3° according to embodiment 1); or to such crystalline form according to any one of embodiments 2) to 5), wherein said form is obtainable by:

a) mixing 2 g of COMPOUND as amorphous material with 8 mL of an ethanol/water mixture with volume/volume ratio of 1/4;
b) adding about 0.05 g seed crystals of COMPOUND in crystalline form 1 (obtainable for example by using the procedure of example 1 below);
c) shaking at 300 rpm for about 16 hours at room temperature;
d) filtering and washing the cake with 2 mL ethanol/water 1/4 (v/v) and drying the product at room temperature and reduced pressure of about 10 mbar for 4 hours; and
e) open equilibration at room temperature and about 60% relative humidity for 2 hours.

7) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3° according to embodiment 1); or to such crystalline form according to any one of embodiments 2) to 6), wherein said crystalline form is a hemi-hydrate (i.e. it contains about 0.5 equivalents of coordinated water per equivalent of COMPOUND; wherein it is understood that said about 0.5 equivalents of coordinated water correspond to a crystalline form having a water content of about 1.96 %.)

8) Another embodiment relates to a crystalline form of COMPOUND according to embodiment 1, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0°.

9) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of

refraction 2θ: 13.4°, 18.3°, and 24.0° according to embodiment 1); or to such crystalline form according to embodiment 8), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 10.9°, 13.4°, 14.3°, 14.9°, 18.3°, 20.9°, 21.1°, 21.8°, 24.0°, and 30.1°.

10) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0° according to embodiment 1); or to such crystalline form according to embodiment 8) or 9), which essentially shows the X-ray powder diffraction pattern as depicted in Figure 3.

11) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0° according to embodiment 1); or to such crystalline form according to any one of embodiments 8) to 10), which has a melting point of about 152°C as determined by differential scanning calorimetry using the method as described herein.

12) In another embodiment the present invention relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0° according to embodiment 1); or to such crystalline form according to any one of embodiments 8) to 11), wherein said form is obtainable by:

a) mixing 10 mg of COMPOUND in crystalline form 1 in 0.05 mL acetonitrile;
b) stirring in a closed 4 mL vial for up to three days;
c) isolating; and drying at reduced pressure (2 mbar) and room temperature for 2 hours.

13) Another embodiment relates to a crystalline form of COMPOUND characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0° according to embodiment 1); or to such crystalline form according to any one of embodiments 8) to 12), wherein said crystalline form is an anhydrate (i.e. it contains no coordinated water).

For avoidance of any doubt, whenever one of the above embodiments refers to "peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ", said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and it should be understood that the accuracy of the 2θ values as provided herein is in the range of +/- 0.1-0.2°. Notably, when specifying an angle of refraction 2theta (2θ) for a peak in the invention embodiments and the claims, the 2θ value given is to be understood

as an interval from said value minus 0.2° to said value plus 0.2° (2θ +/- 0.2°); and preferably from said value minus 0.1° to said value plus 0.1° (2θ +/- 0.1°).

Where the plural form is used for compounds, solid, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, solid, or the like.

The term “enantiomerically enriched” is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the COMPOUND are present in form of one enantiomer of the COMPOUND. It is understood that COMPOUND is present in enantiomerically enriched absolute (S)-configuration.

The term “essentially pure” is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the crystals of a COMPOUND are present in a crystalline form according to the present invention, especially in a single crystalline form of the present invention.

When defining the presence of peak in e.g. an X-ray powder diffraction diagram, a common approach is to do this in terms of the S/N ratio (S = signal, N = noise). According to this definition, when stating that a peak has to be present in an X-ray powder diffraction diagram, it is understood that the peak in the X-ray powder diffraction diagram is defined by having an S/N ratio (S = signal, N = noise) of greater than x (x being a numerical value greater than 1), usually greater than 2, especially greater than 3.

In the context with stating that the crystalline form essentially shows an X-ray powder diffraction pattern as depicted in Fig. 2 or Fig. 3, respectively, the term "essentially" means that at least the major peaks of the diagram depicted in said figures, i.e. those having a relative intensity of more than 10%, especially more than 20%, as compared to the most intense peak in the diagram, have to be present. However, the person skilled in the art of X-ray powder diffraction will recognize that relative intensities in X-ray powder diffraction diagrams may be subject to strong intensity variations due to preferred orientation effects.

Unless used regarding temperatures, the term “about” placed before a numerical value “X” refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term “about” placed before a temperature “Y” refers in the current application to an interval extending from the temperature Y minus 10 ºC to Y plus 10 ºC, preferably to an interval extending from Y minus 5 ºC to Y plus 5 ºC, notably to an interval extending from Y minus 3 ºC to Y plus 3 ºC. Room temperature means a temperature of about 25 ºC. When in the current application the term n equivalent(s) is used

wherein n is a number, it is meant and within the scope of the current application that n is referring to about the number n, preferably n is referring to the exact number n.

Whenever the word “between” or "to" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40ºC and 80ºC (or 40ºC to 80ºC), this means that the end points 40ºC and 80ºC are included in the range; or if a variable is defined as being an integer between 1 and 4 (or 1 to 4), this means that the variable is the integer 1, 2, 3, or 4.

The expression % w/w refers to a percentage by weight compared to the total weight of the composition considered. Likewise, the expression v/v refers to a ratio by volume of the two components considered. The expression "vol" signifies volumes (in L, e.g. of solvent) per weight (in kg, e.g. of reactant). For example 7 vol signifies 7 liters (of solvent) per kg (of reactant).

The crystalline forms, especially the essentially pure crystalline forms, of COMPOUND according to any one of embodiments 1) to 13) can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

12) Another embodiment thus relates to a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of embodiments 1) to 13) for use as a medicament.

The crystalline solid, especially the essentially pure crystalline solid, of COMPOUND according to any one of embodiments 1) to 13) may be used as single component or as mixtures with other crystalline forms or the amorphous form of COMPOUND.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, “Pharmaceutical Manufacturing” [published by Lippincott Williams & Wilkins]) by bringing the crystalline forms of the present invention, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

14) A further embodiment of the invention relates to pharmaceutical compositions comprising as active ingredient a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-

yl)phenyl)methanone according to any one of embodiments 1) to 13), and at least one pharmaceutically acceptable carrier material.

Such pharmaceutical compositions according to embodiment 14) are especially useful for the prevention or treatment of diseases or disorders related to the orexin system, such as especially sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders.

15) A further embodiment of the invention relates to a pharmaceutical composition according to embodiment 14), wherein said pharmaceutical composition is in form of a tablet.

16) A further embodiment of the invention relates to a pharmaceutical composition according to embodiment 14), wherein said pharmaceutical composition is in form of a capsule.

17) A further embodiment of the invention relates to a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of embodiments 1) to 13) [especially the crystalline form according to any one of embodiments 2) to 7)], for use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone, and at least one pharmaceutically acceptable carrier material.

For avoidance of any doubt, embodiment 17) refers to the crystalline form according to any one of embodiments 1) to 13) [especially the crystalline form according to any one of embodiments 2) to 7)] which is suitable / which is used as final isolation step of COMPOUND (e.g. in order to meet the purity requirements of pharmaceutical production), whereas the final pharmaceutical composition according to embodiment 17) may or may not contain said crystalline form (e.g. because the originally crystalline form of COMPOUND is further transformed during the manufacturing process and / or is dissolved in the pharmaceutically acceptable carrier material(s); thus, in the final pharmaceutical composition, COMPOUND may be present in non-crystalline form, in another crystalline form, or in dissolved form, or the like).

18) A further embodiment of the invention thus relates to a pharmaceutical composition comprising as active ingredient the COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone, wherein said pharmaceutical composition is manufactured using a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any

one of embodiments 1) to 13) [especially the crystalline form according to any one of embodiments 2) to 7)] and at least one pharmaceutically acceptable carrier material.

19) A further embodiment of the invention relates to a pharmaceutical composition according to embodiment 18), wherein said pharmaceutical composition is in form of a capsule.

20) A further embodiment of the invention relates to a pharmaceutical composition according to embodiments 18) or 19), wherein such pharmaceutical composition is a lipid-based formulation (for reference see for example C.W. Pouton, C.J.H. Porter, Advanced Drug Delivery Reviews 60 (2008) 625–637, the disclosure of which is fully incorporated).

21) A further embodiment of the invention relates to a pharmaceutical composition according to embodiments 18), wherein such pharmaceutical composition is a solid amorphous dispersion.

22) A further embodiment of the invention relates to a pharmaceutical composition according to embodiment 21), wherein said pharmaceutical composition is in form of a tablet, or in form of a capsule.

Such pharmaceutical compositions according to embodiments 18) to 22) are especially useful for the prevention or treatment of diseases or disorders related to the orexin system, such as sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders; especially for the prevention or treatment of diseases or disorders above where a short onset of action is required (as especially sleep disorders or anxiety disorders).

23) A further embodiment of the invention relates to a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of embodiments 1) to 13), for use in the prevention or treatment of diseases or disorders related to the orexin system, notably mental health diseases or disorders relating to orexinergic dysfunctions.

24) A further embodiment of the invention relates to a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of embodiments 1) to 13), for use in the preparation of a medicament for the prevention or treatment of diseases or disorders related to the orexin system, notably mental health diseases or disorders relating to orexinergic dysfunctions.

25) A further embodiment of the invention relates to pharmaceutical compositions according to any one of embodiments 14) to 16), or 18) to 22), for the prevention or treatment of

diseases or disorders related to the orexin system, notably mental health diseases or disorders relating to orexinergic dysfunctions.

26) A further embodiment of the invention relates to any one of embodiments 23) to 25), wherein said diseases or disorders related to the orexin system are mental health diseases or disorders relating to orexinergic dysfunctions selected from the group consisting of sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, and appetite disorders (especially sleep disorders, anxiety disorders, and addiction disorders).

25) A further embodiment of the invention relates to any one of embodiments 22) to 25), wherein said diseases or disorders related to the orexin system are mental health diseases or disorders relating to orexinergic dysfunctions selected from the group consisting of sleep disorders selected from the group consisting of dyssomnias, parasomnias, sleep disorders associated with a general medical condition and substance-induced sleep disorders; anxiety disorders; and addiction disorders.

Such disorders relating to orexinergic dysfunctions are diseases or disorders where an antagonist of a human orexin receptor is required, notably mental health disorders relating to orexinergic dysfunctions. The above mentioned disorders may in particular be defined as comprising sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders. In one sub-embodiment, the above mentioned disorders comprise especially anxiety disorders, addiction disorders and mood disorders, notably anxiety disorders and addiction disorders. In another sub-embodiment, the above mentioned disorders comprise especially sleep disorders.

In addition, further disorders relating to orexinergic dysfunctions are selected from treating, controlling, ameliorating or reducing the risk of epilepsy, including absence epilepsy; treating or controlling pain, including neuropathic pain; treating or controlling Parkinson's disease; treating or controlling psychosis including acute mania and bipolar disorder; treating or controlling stroke, particularly ischemic or haemorrhagic stroke; blocking an emetic response i.e. nausea and vomiting; and treating or controlling agitation, in isolation or co-morbid with another medical condition.

Anxiety disorders can be distinguished by the primary object or specificity of threat, ranging from rather diffuse as in generalized anxiety disorder, to circumscribed as encountered in phobic anxieties (PHOBs) or post-traumatic stress disorders (PTSDs). Anxiety disorders may, thus, be defined as comprising generalized anxiety disorders (GAD), obsessive compulsive disorders (OCDs), acute stress disorders, posttraumatic stress disorders (PTSDs), panic anxiety disorders (PADs) including panic attacks, phobic anxieties (PHOBs), specific phobia, social phobia (social anxiety disorder), avoidance, somatoform disorders

including hypochondriasis, separation anxiety disorder, anxiety disorders due to a general medical condition, and substance induced anxiety disorders. In a sub-embodiment, particular examples of circumscribed threat induced anxiety disorders are phobic anxieties or post-traumatic stress disorders. Anxiety disorders especially include post-traumatic stress disorders, obsessive compulsive disorders, panic attacks, phobic anxieties, and avoidance.

Addiction disorders may be defined as addictions to one or more rewarding stimuli, notably to one rewarding stimulus. Such rewarding stimuli may be of either natural or synthetic origin. Examples of such rewarding stimuli are substances / drugs {of either natural or synthetic origin; such as cocaine, amphetamines, opiates [of natural or (semi-)synthetic origin such as morphine or heroin], cannabis, ethanol, mescaline, nicotine, and the like}, which substances / drugs may be consumed alone or in combination; or other rewarding stimuli {of either natural origin (such as food, sweet, fat, or sex, and the like), or synthetic origin [such as gambling, or internet/IT (such as immoderate gaming, or inappropriate involvement in online social networking sites or blogging), and the like]}. In a sub-embodiment, addiction disorders relating to psychoactive substance use, abuse, seeking and reinstatement are defined as all types of psychological or physical addictions and their related tolerance and dependence components. Substance-related addiction disorders especially include substance use disorders such as substance dependence, substance craving and substance abuse; substance-induced disorders such as substance intoxication, substance withdrawal, and substance-induced delirium. The expression "prevention or treatment of addictions" (i.e. preventive or curative treatment of patients who have been diagnosed as having an addiction, or as being at risk of developing addictions) refers to diminishing addictions, notably diminishing the onset of addictions, to weakening their maintenance, to facilitating withdrawal, to facilitating abstinence, or to attenuating, decreasing or preventing the occurrence of reinstatement of addiction (especially to diminishing the onset of addictions, to facilitating withdrawal, or to attenuating, decreasing or preventing the occurrence of reinstatement of addiction).

Mood disorders include major depressive episode, manic episode, mixed episode and hypomanic episode; depressive disorders including major depressive disorder, dysthymic disorders; bipolar disorders including bipolar I disorder, bipolar II disorder (recurrent major depressive episodes with hypomanic episodes), cyclothymic disorder; mood disorders including mood disorder due to a general medical condition (including the subtypes with depressive features, with major depressive-like episode, with manic features, and with mixed features), substance-induced mood disorder (including the subtypes with depressive features, with manic features, and with mixed features). Such mood disorders are especially

major depressive episode, major depressive disorder, mood disorder due to a general medical condition; and substance-induced mood disorder.

Appetite disorders comprise eating disorders and drinking disorders. Eating disorders may be defined as comprising eating disorders associated with excessive food intake and complications associated therewith; anorexias; compulsive eating disorders; obesity (due to any cause, whether genetic or environmental); obesity-related disorders including overeating and obesity observed in Type 2 (non-insulin-dependent) diabetes patients; bulimias including bulimia nervosa; cachexia; and binge eating disorder. Particular eating disorders comprise metabolic dysfunction; dysregulated appetite control; compulsive obesities; bulimia or anorexia nervosa. In a sub-embodiment, eating disorders may be defined as especially comprising anorexia nervosa, bulimia, cachexia, binge eating disorder, or compulsive obesities. Drinking disorders include polydipsias in psychiatric disorders and all other types of excessive fluid intake. Pathologically modified food intake may result from disturbed appetite (attraction or aversion for food); altered energy balance (intake vs. expenditure); disturbed perception of food quality (high fat or carbohydrates, high palatability); disturbed food availability (unrestricted diet or deprivation) or disrupted water balance.

Cognitive dysfunctions include deficits in attention, learning and especially memory functions occurring transiently or chronically in psychiatric, neurologic, neurodegenerative, cardiovascular and immune disorders, and also occurring transiently or chronically in the normal, healthy, young, adult, or especially aging population. Cognitive dysfunctions especially relate to the enhancement or maintenance of memory in patients who have been diagnosed as having, or being at risk of developing, diseases or disorders in which diminished memory (notably declarative or procedural) is a symptom [in particular dementias such as frontotemporal dementia, or dementia with Lewy bodies, or (especially) Alzheimer's disease]. Especially, the term "prevention or treatment of cognitive dysfunctions" relates to the enhancement or maintenance of memory in patients who have a clinical manifestation of a cognitive dysfunction, especially expressed as a deficit of declarative memory, linked to dementias such as frontotemporal dementia, or dementia with Lewy bodies, or (especially) Alzheimer's disease. Furthermore, the term "prevention or treatment of cognitive dysfunctions" also relates to improving memory consolidation in any of the above mentioned patient populations.

Sleep disorders comprise dyssomnias, parasomnias, sleep disorders associated with a general medical condition and substance-induced sleep disorders. In particular, dyssomnias include intrinsic sleep disorders (especially insomnias, breathing-related sleep disorders, periodic limb movement disorder, and restless leg syndrome), extrinsic sleep disorders, and

circadian-rythm sleep disorders. Dyssomnias notably include insomnia, primary insomnia, idiopathic insomnia, insomnias associated with depression, emotional/mood disorders, aging, Alzheimer's disease or cognitive impairment; REM sleep interruptions; breathing-related sleep disorders; sleep apnea; periodic limb movement disorder (nocturnal myoclonus), restless leg syndrome, circadian rhythm sleep disorder; shift work sleep disorder; and jet-lag syndrome. Parasomnias include arousal disorders and sleep-wake transition disorders; notably parasomnias include nightmare disorder, sleep terror disorder, and sleepwalking disorder. Sleep disorders associated with a general medical condition are in particular sleep disorders associated with diseases such as mental disorders, neurological disorders, neuropathic pain, and heart and lung diseases. Substance-induced sleep disorders include especially the subtypes insomnia type, parasomnia type and mixed type, and notably include conditions due to drugs which cause reductions in REM sleep as a side effect. Sleep disorders especially include all types of insomnias, sleep-related dystonias; restless leg syndrome; sleep apneas; jet-lag syndrome; shift work sleep disorder, delayed or advanced sleep phase syndrome, or insomnias related to psychiatric disorders. In addition, sleep disorders further include sleep disorders associated with aging; intermittent treatment of chronic insomnia; situational transient insomnia (new environment, noise) or short-term insomnia due to stress; grief; pain or illness.

In the context of the present invention, it is to be understood that, in case certain environmental conditions such as stress or fear (wherein stress may be of social origin (e.g. social stress) or of physical origin (e.g. physical stress), including stress caused by fear) facilitate or precipitate any of the disorders or diseases as defined before, the present compounds may be particularly useful for the treatment of such environmentally conditioned disorder or disease.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein, comprising administering to a subject a pharmaceutically active amount of a crystalline form of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of embodiments 1) to 13), or of a pharmaceutical composition according to any one of embodiments 14) to 16, or 18) to 20).

The present invention also relates to a process for the preparation of COMPOUND in enantiomerically enriched form, and to processes for the preparation and characterization of the crystalline forms of COMPOUND (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any

one of embodiments 1) to 13). Said processes are described in embodiments 6) and 12), as well as in the procedures of the experimental part below.

Experimental Procedures:

Abbreviations (as used hereinbefore or hereinafter):

Ac	Acetyl (such as in OAc = acetate, AcOH = acetic acid)
AcOH	Acetic acid
anh.	Anhydrous
aq.	aqueous
atm	Atmosphere
tBME	tert-Butylmethylether
Boc	*tert*-Butoxycarbonyl
Boc_2O	di-*tert*-Butyl dicarbonate
BSA	Bovine serum albumine
Bu	Butyl such as in tBu = *tert*-butyl = tertiary butyl
CC	Column Chromatography on silica gel
CHO	Chinese Hamster Ovary
conc.	Concentrated
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEA	Diethylamine
DIPEA	Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	
ELSD	Evaporative Light-Scattering Detection
eq	Equivalent(s)
ES	Electron spray
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Ex.	Example
FC	Flash Chromatography on silica gel
FCS	Foatal calf serum
Fig	Figure

FLIPR	Fluorescent imaging plate reader
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBSS	Hank's balanced salt solution
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
^{1}H-NMR	Nuclear magnetic resonance of the proton
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography – Mass Spectroscopy
Lit.	Literature
M	Exact mass (as used for LC-MS)
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MeI	Methyl iodide
MHz	Megahertz
µl	microliter
min	Minute(s)
MS	Mass spectroscopy
N	Normality
$Pd(OAc)_2$	Palladium diacetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PL-HCO_3	Polymer supported hydrogen carbonate
Ph	Phenyl
PPh_3	Triphenylphosphine
prep.	Preparative
RH	relative humidity
RT	Room temperature
sat.	Saturated
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TFA	trifluoroacetic acid
Tf	Trifluoromethansulfonyl
THF	Tetrahydrofuran
t_R	Retention time

UV Ultra violet

I-Chemistry

All temperatures are stated in °C. The commercially available starting materials were used as received without further purification. Compounds are purified by flash column chromatography on silica gel (FC) or by preparative HPLC. Compounds described in the invention are characterized by LC-MS (retention time t_R is given in min.; molecular weight obtained from the mass spectrum is given in g/mol, using the conditions listed below). If the mass is not detectable the compounds are also characterized by ^{1}H-NMR (400 MHz: Bruker; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; p = pentuplet, hex = hexet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz).

Preparative HPLC for purification of compounds (conditions C)

Column: Waters XBridge (10 μm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH_4OH (25% aq.) [eluent B]; Gradient: 90% B → 5% B over 6.5 min. (flow: 75 ml/min.). Detection: UV + ELSD.

Preparative HPLC for purification of compounds (conditions D)

Column: Waters Atlantis T3 OBD (10 μm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCOOH [eluent B]; Gradient: 90% B → 5% B over 6.4 min. (flow: 75 ml/min.). Detection: UV + ELSD.

LC-MS with acidic conditions

Apparatus: Agilent 1100 series with mass spectroscopy detection (MS : Finnigan single quadrupole). Column: Agilent Zorbax SB-Aq, (3.5 um, 4.6 x 50mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV + MS.

X-ray powder diffraction analysis (XRPD)

X-ray powder diffraction patterns were collected on a Bruker D8 Advance X-ray diffractometer equipped with a Lynxeye detector operated with CuK_a-radiation in reflection mode (coupled two Theta/Theta). Typically, the X-ray tube was run at of 40kV/40mA. A step size of 0.02° (2θ) and a step time of 76.8 sec over a scanning range of 3 - 50° in 2θ were applied. The divergence slit was set to fixed 0.3. Powders were slightly pressed into a silicon single crystal sample holder with depth of 0.5 mm and samples were rotated in their own

plane during the measurement. Diffraction data are reported using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping. The accuracy of the 2θ values as provided herein is in the range of +/- 0.1-0.2° as it is generally the case for conventionally recorded X-ray powder diffraction patterns.

Gravimetric vapour sorption (GVS) analysis

Measurements were performed simoultaneously for the COMPOUND amorphous free base and the COMPOUND crystalline form 1 and crystalline form 2 on a multi sample instrument SPS-100n (Projekt Messtechnik, Ulm, Germany) operated in stepping mode at 25°C. The sample was allowed to equilibrate at 40% RH before starting a pre-defined humidity program (40-0-95-0-95-40% RH, steps of 5% ΔRH and with a maximal equilibration time of 24 hours per step were applied. About 20 to 30 mg of each sample was used. The hygroscopic classification is done according to the European Pharmacopeia Technical Guide (1999, page 86), e.g., slightly hygroscopic: increase in mass is less than 2% and equal to or greater than 0.2% mass/mass; hygroscopic: increase in mass is less than 15% and equal to or greater than 2% mass/mass. The mass change between 40% relative humidity and 80% relative humidity in the first adsorption scan is considered.

Differential scanning calorimetry (DSC)

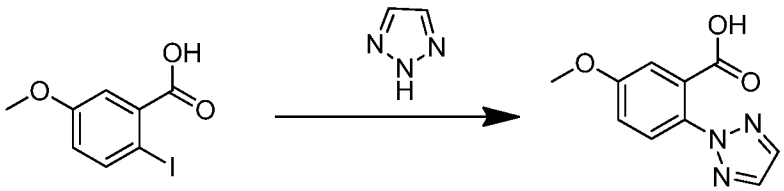
DSC data were collected on a Mettler Toledo STARe System (DSC822e module, measuring cell with ceramic sensor and STAR software version 9.20) equipped with a 34 position auto-sampler. The instrument was calibrated for energy and temperature using certified indium. Typically 1-5 mg of each sample, in an automatically pierced aluminium pan, was heated at 10°C min^{-1}, unless stated otherwise, from -20°C to 280°C. A nitrogen purge at 20 ml min^{-1} was maintained over the sample. Peak temperatures are reported for melting points.

Thermogravimetric analysis (TGA)

TGA data were collected on a Mettler Toledo STARe System (TGA851e module and STAR software version 9.20) equipped with a 34 position auto-sampler. Typically about 5 mg of a sample, in an automatically pierced aluminium pan, was heated at 10°C min^{-1}, unless stated otherwise, from 30°C to 250°C. A nitrogen purge at 10 ml min^{-1} was maintained over the sample.

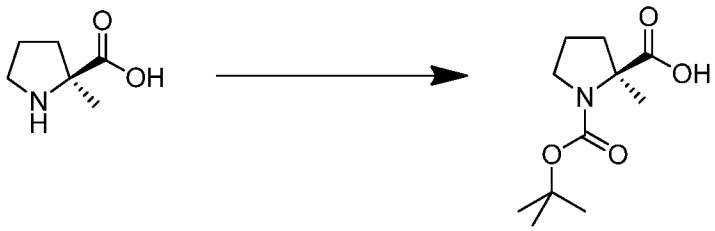
Reference Example 1

1) Synthesis of 5-methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic acid



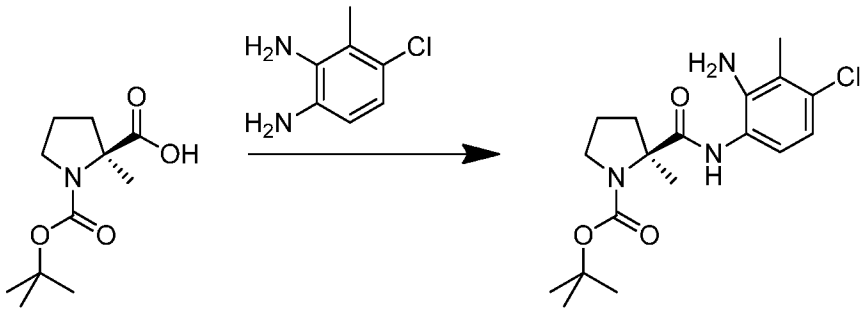
2-Iodo-5-methoxy benzoic acid (15.0 g; 53.9 mmol) is dissolved in anhydrous DMF (45 ml) followed by the addition of 1H-1,2,3-triazole (7.452 g; 108 mmol) and cesium carbonate (35.155 g; 108 mmol). By the addition of cesium carbonate the temperature of the reaction mixture increases to 40°C and gas evolved from the reaction mixture. Copper(I)iodide (514 mg; 2.7 mmol) is added. This triggers a strongly exothermic reaction and the temperature of the reaction mixture reaches 70°C within a few seconds. Stirring is continued for 30 minutes. Then the DMF is evaporated under reduced pressure followed by the addition of water (170 ml) and EtOAc (90 ml). The mixture is vigorously stirred and by the addition of citric acid monohydrate the pH is adjusted to 3-4. The precipitate is filtered off and washed with water and EtOAc and discarded. The filtrate is poured into a separation funnel and the phases are separated. The water phase is extracted again with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated to give 7.1 g of 5-methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic acid as a white powder of 94% purity (6 % impurity is the regioisomerically N1-linked triazolo-derivative); t_R [min] = 0.60; $[M+H]^+$ = 220.21

2) Synthesis of (S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid



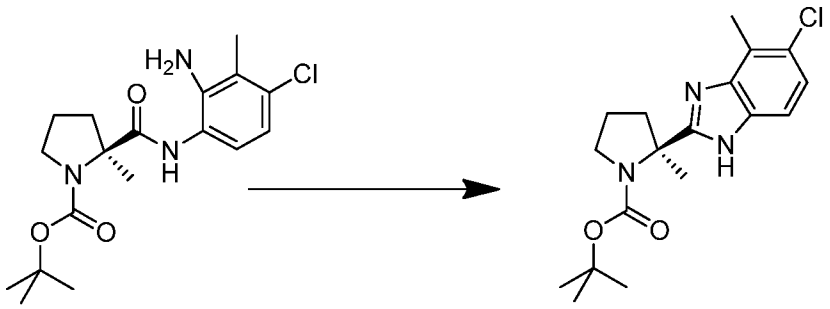
2-Methyl-L-proline hydrochloride (99.7 g; 602 mmol) is dissolved in a 1/1-mixture of MeCN and water (800 ml) and triethylamine (254 ml; 1810 mmol) is added. The temperature of the reaction mixture slightly rises. The reaction mixture is cooled to 10°C to 15°C followed by careful addition of a solution of Boc_2O (145 g; 662 mmol) in MeCN (200 ml) over 10 minutes. Stirring at RT is continued for 2 hours. The MeCN is evaporated under reduced pressure and aq. NaOH solution (2M; 250 ml) is added to the residual aq. part of the reaction mixture. The water layer is washed with Et_2O (2x 300 ml) then cooled to 0°C followed by slow and careful addition of aq. HCl (25%) to adjust the pH to 2. During this procedure a suspension forms. The precipitate is filtered off and dried at HV to give 110.9 g of the title compound as a beige powder; t_R [min] = 0.68; $[M+H]^+$ = 230.14

3) Synthesis of (S)-tert-butyl 2-((2-amino-4-chloro-3-methylphenyl)carbamoyl)-2-methylpyrrolidine-1-carboxylate



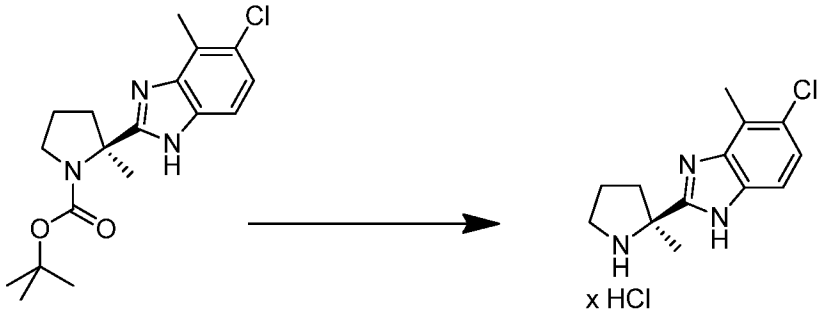
(S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (60 g; 262 mmol) and HATU (100 g; 264 mmol) is suspended in DCM (600 ml) followed by the addition of DIPEA (84.6 g; 654 mmol) and 6-chloro-2,3-diaminotoluene (41 g; 262 mmol). The reaction mixture is stirred at rt for 14 hours then concentrated under reduced pressure and to the residue is added water followed by the extraction of the product with EtOAc (3x). The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure to give 185 g of the title compound as a dark brownish oil, which is used in the next step without further purification; t_R [min] = 0.89; $[M+H]^+$ = 368.01

4) Synthesis of (S)-tert-butyl 2-(5-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate



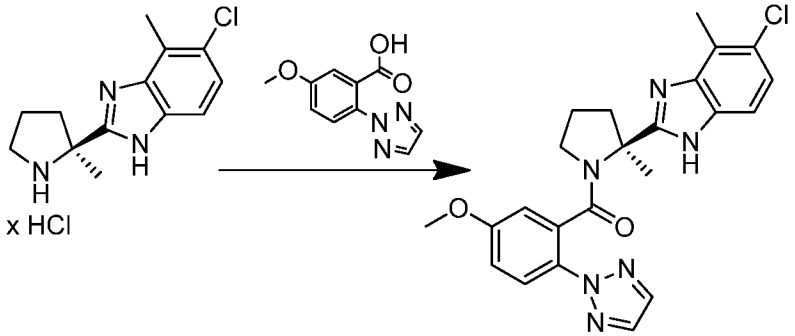
(S)-tert-butyl 2-((2-amino-4-chloro-3-methylphenyl)carbamoyl)-2-methylpyrrolidine-1-carboxylate (185 g; 427 mmol) are dissolved in AcOH (100%; 611 ml), heated to 100°C and stirring continued for 90 minutes. The AcOH is evaporated under reduced pressure and the residue is dissolved in DCM followed by careful addition of saturated sodium bicarbonate solution. The phases are separated, the aq. phase is extracted once more with DCM, the combined aq. phases are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure to give 142.92 g of the title compound as a dark brown oil which is used in the next step without further purification; t_R [min] = 0.69; $[M+H]^+$ = 350.04

5) Synthesis of (S)-5-chloro-4-methyl-2-(2-methylpyrrolidin-2-yl)-1H-benzo[d]imidazole hydrochloride



(S)-tert-butyl 2-(5-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (355.53 g; 1.02 mol) are dissolved in dioxane (750 ml) followed by careful addition of HCl solution in dioxane (4M; 750 ml; 3.05 mol). The reaction mixture is stirred for 3 hours followed by the addition of Et_2O (800 ml) which triggered precipitation of the product. The solid is filtered off and dried at high vacuum to give 298.84 g of the title compound as a redish powder; t_R [min] = 0.59; $[M+H]^+$ = 250.23

6) Synthesis of [(S)-2-(5-chloro-4-methyl-1H-benzoimidazol-2-yl)-2-methyl-pyrrolidin-1-yl]-(5-methoxy-2-[1,2,3]triazol-2-yl-phenyl)-methanone



(S)-5-chloro-4-methyl-2-(2-methylpyrrolidin-2-yl)-1H-benzo[d]imidazole hydrochloride (62.8 g; 121 mmol) is dissolved in DCM (750 ml) followed by the addition of 5-methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic acid (62.8 g; 121 mmol) and DIPEA (103 ml; 603 mmol). Stirring is continued for 10 minutes followed by the addition of HATU (47 g; 124 mmol). The reaction mixture is stirred for 16 hours at RT. The solvents are evaporated under reduced pressure and the residue is dissolved in EtOAc (1000 ml) and washed with water (3x 750 ml). The organic phase is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The residue is purified by CC with EtOAc / hexane = 2 / 1to give 36.68 g of the title compound as an amorphous white powder. t_R [min] = 0.73; $[M+H]^+$ = 450.96

Table 1: Characterisation data for COMPOUND as free base in amorphous form

Technique	Data Summary	Remarks
XRPD	Amorphous	see Fig. 1
Elemental analysis	Consistent.	
Hygroscopicity	Slightly hygroscopic (mass change of about 0.7%), Hysteresis and sorption of up to 2.7% moisture mass/mass. Variability in sorption behavior first to second cycle	see Fig. 4

II. Preparation of crystalline forms of COMPOUND

Example 1: Preparation and characterization of COMPOUND in crystalline form 1

a) Preparation of seeding material of COMPOUND in crystalline Form 1

0.2 g of COMPOUND as amorphous material was dissolved in 2 mL of MeOH in a 7 mL vial. The sample was left open at ambient and evaporated over weekend. An amorphous mass with some few crystals was obtained as observed under crossed polars. 0.05 mL MeOH was added, the vial was closed and the sample was sonicated for 1 minute and heated to 40°C. Repeating such procedure 3 to 4 times lead to further crystallization and after about 15 min the sample was further shaken at 25°C for 1h. Thereafter the solid was isolated, dried at reduced pressure (2 mbar, room temperature) for 4 hours and allowed to equilibrate open at room temperature and 58% relative humidity for 2 hours. An off white powder was obtained which is COMPOUND in crystalline form 1. It might be necessary to repeat such procedure several times to obtain sufficient material to be used for seeding.

Alternatively, 0.4 mL of an ethanol/water mixture with volume/volume ratio of 1/4 can be added to 0.1 g of COMPOUND as amorphous material. Such mixture is allowed to stand closed for up to three days. Isolation, drying and equilibration as described above results in COMPOUND in crystalline form 1

b) Preparation of COMPOUND in crystalline Form 1

2 g of COMPOUND is mixed with 8 mL of an ethanol/water mixture with volume/volume ratio of 1/4 and about 0.05 g of seeds obtained with a procedure as described above. The sample is shaken overnight at room temperature and the solid was isolated, dried at reduced pressure (2 mbar, room temperature) for 4hours and allowed to equilibrate open at room temperature and 58% relative humidity for 2 hours. An off white powder was obtained which is COMPOUND in crystalline form 1.

Table 2: Characterisation data for COMPOUND in crystalline form 1

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 2
1H-NMR	Consistent	
DSC	broad endothermal event in the range of about 50 to 160°C	
TGA	Mass loss of 2.0% in the range 30 to 170°C	
Hygroscopicity	Non hygroscopic (mass change smaller then 0.1%)	See Fig. 5

Example 2: Preparation and characterization of COMPOUND in crystalline form 2

0.05 mL of acetonitrile and 0.01 g of COMPOUND in crystalline form 1 are mixed with a magnetic stirrer in a 4 mL glass at room temperature for up to 3 days. The solid is isolated and dried under reduced pressure (30 min at 2mbar) and the solid is COMPOUND is crystalline form 2.

Alternatively 0.1 mL of methyl-isobutylketone and 0.015 g of COMPOUND in crystalline form 1 are mixed with a magnetic stirrer in a 4 mL glass at room temperature for up to 3 days. The solid is isolated and dried under reduced pressure (2 hours at 2mbar) and the solid is COMPOUND is crystalline form 2.

Table 3: Characterisation data for COMPOUND in crystalline form 2

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 3
1H-NMR	Consistent	
DSC	Melt endotherm with melting point at about 152°C	
Hygroscopicity	Slightly hygroscopic (mass change of about 0.7%) Hysteresis and sorption of up to 1.1% moisture mass/mass.	See Fig. 6

III. Biological assays

To further characterize the biological activity of COMPOUND, antagonistic activities on both orexin receptors have been measured using the following procedure:

In vitro assay: Intracellular calcium measurements:

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor and the human orexin-2 receptor, respectively, are grown in culture medium (Ham F-12 with L-Glutamine) containing 300 μg/ml G418, 100 U/ml penicillin, 100 μg/ml streptomycin and 10 % heat inactivated fetal calf serum (FCS). The cells are seeded at 20'000 cells / well into 384-well black clear bottom sterile plates (Greiner). The seeded plates are incubated overnight at 37°C in 5% CO_2.

Human orexin-A as an agonist is prepared as 1 mM stock solution in MeOH: water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA), $NaHCO_3$: 0.375g/l and 20 mM HEPES for use in the assay at a final concentration of 3 nM.

Antagonists are prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates using DMSO followed by a transfer of the dilutions into in HBSS containing 0.1 % bovine serum albumin (BSA), $NaHCO_3$: 0.375g/l and 20 mM HEPES. On the day of the assay, 50 μl of staining buffer (HBSS containing 1% FCS, 20 mM HEPES, $NaHCO_3$: 0.375g/l, 5 mM probenecid (Sigma) and 3 μM of the fluorescent calcium indicator fluo-4 AM (1 mM stock solution in DMSO, containing 10% pluronic) is added to each well. The 384-well cell-plates are incubated for 50 min at 37° C in 5% CO_2 followed by equilibration at RT for 30 min before measurement.

Within the Fluorescent Imaging Plate Reader (FLIPR Tetra, Molecular Devices), antagonists are added to the plate in a volume of 10 μl/well, incubated for 120 min and finally 10 μl/well of agonist is added. Fluorescence is measured for each well at 1 second intervals, and the height of each fluorescence peak is compared to the height of the fluorescence peak induced by an approximate EC_{70} (for example 5 nM) of orexin-A with vehicle in place of antagonist. The IC_{50} value (the concentration of compound needed to inhibit 50 % of the agonistic response) is determined and may be normalized using the obtained IC_{50} value of a on-plate reference compound. Optimized conditions are achieved by adjustment of pipetting speed and cell splitting regime. The calculated IC_{50} values may fluctuate depending on the daily cellular assay performance. Fluctuations of this kind are known to those skilled in the art. Average IC_{50} values from several measurements are given as mean values.

COMPOUND has been measured on the orexin-1 receptor with an IC_{50} value of 2 nM.

COMPOUND has been measured on the orexin-2 receptor with an IC_{50} value of 3 nM.

Measurement of brain and systemic concentration after oral administration:

In order to assess brain penetration, the concentration of the compound is measured in plasma ([P]), and brain ([B]), sampled 3 h (or at different time points) following oral administration (e.g. 100 mg/kg) to male wistar rats. The compound is formulated e.g. in 100% PEG 400. Samples are collected in the same animal at the same time point (+/- 5 min). Blood is sampled from the vena cava caudalis into containers with EDTA as anticoagulant and centrifuged to yield plasma. Brain is sampled after cardiac perfusion of 10 mL NaCl 0.9% and homogenized into one volume of cold phosphate buffer (pH 7.4). All samples are extracted with MeOH and analyzed by LC-MS/MS. Concentrations are determined with the help of calibration curves.

Results obtained for COMPOUND:
3 h after oral administration (100 mg/kg), n = 3): [P] = 1280 ng / ml; [B] = 1808 ng / g.

Sedative effects: EEG, EMG and behavioural indices of alertness recorded by radiotelemetry in vivo in Wistar rats.

Electroencephalography (EEG) and Electromyography (EMG) signals were measured by telemetry using TL11M2-F20-EET miniature radiotelemetric implants (Data Science Int.) with two pairs of differential leads.

Surgical implantation was performed under general anesthesia with Ketamin/Xylazin, for cranial placement of one differential pair of EEG electrodes and one pair of EMG leads inserted in either side of the muscles of the neck. After surgery, rats recovered in a thermoregulated chamber and received analgesic treatment with subcutaneous buprenorphine twice a day for 2 d. They were then housed individually and allowed to recover for a minimum of 2 weeks. Thereafter, rats—in their home cage—were placed in a ventilated sound-attenuating box, on a 12-h light / 12-h dark cycle, for acclimatization before continuous EEG / EMG recordings started. The telemetric technology that we used in this study allows accurate and stress-free acquisition of biosignals in rats placed in their familiar home cage environment, with no recording leads restricting their movements. Variables analyzed included four different stages of vigilance and sleep, spontaneous activity in the home cage and body temperature. Sleep and wake stages were evaluated using a rodent

scoring software (Somnologica Science) directly processing electrical biosignals on 10 s contiguous epochs. The scoring is based on frequency estimation for EEG and amplitude discrimination for EMG and locomotor activity. Using these measurements, the software determines the probability that all components within each epoch best represent active waking (AW), quiet waking (QW), non-REM-sleep (NREM) or REM-sleep (REM). The percentage of total time spent in AW, QW, NREM- and REM-sleep was calculated per 12 h light or dark period. The latency to the onset of the first significant NREM- and REM-sleep episodes and the frequency and duration of those episodes were also calculated. AW, QW, NREM- and REM-sleep, home cage activity and body temperature were measured at baseline for at least one total circadian cycle (12 h-night, 12 h-day) before a test compound was administered. If baseline measurements indicated that animals were stable, test compound or vehicle was given in the evening by oral gavage at the end of the baseline 12-h day period, immediately before the nocturnal rise in orexin and activity in rats. All variables were subsequently recorded for 12 h following administration of the orexin receptor antagonist.

COMPOUND has been tested in this assay (oral dosage: 30 mg/kg po; effects analyzed over 6 hours): Results are: -24% on active wake, -31% on home cage activity, +27% on NREM sleep, +53% on REM sleep; when compared to vehicle controls.

Claims

1. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone; characterized by:

- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3°; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0°.

2. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claim 1, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 8.6°, 15.2°, and 21.3°.; wherein said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and the accuracy of the 2θ values is in the range of 2θ +/- 0.2°.

3. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claim 1, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: θ: 8.6°, 11.5°, 13.4°, 14.6°, 15.2°, 15.5°, 19.3°, 21.3°, 22.4°, and 26.4°.; wherein said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and the accuracy of the 2θ values is in the range of 2θ +/- 0.2°.

4. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claims 2 or 3, which essentially shows the X-ray powder diffraction pattern as depicted in Figure 2.

5. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 2 to 4, wherein said crystalline form is a hemi-hydrate.

6. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 2 to 5, obtainable by:

a) mixing 2 g of COMPOUND as amorphous material with 8 mL of an ethanol/water mixture with volume/volume ratio of 1/4;
b) adding about 0.05 g seed crystals of COMPOUND in crystalline form 1;

c) shaking at 300 rpm for about 16 hours at room temperature;

d) filtering and washing the cake with 2 mL ethanol/water 1/4 (v/v) and drying the product at room temperature and reduced pressure of about 10 mbar for 4 hours; and

e) open equilibration at room temperature and about 60% relative humidity for 2 hours.

7. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claim 1, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 13.4°, 18.3°, and 24.0°.; wherein said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and the accuracy of the 2θ values is in the range of 2θ +/- 0.2°.

8. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claim 1, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 10.9°, 13.4°, 14.3°, 14.9°, 18.3°, 20.9°, 21.1°, 21.8°, 24.0°, and 30.1°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and the accuracy of the 2θ values is in the range of 2θ +/- 0.2°.

9. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to claims 7 or 8, which essentially shows the X-ray powder diffraction pattern as depicted in Figure 3.

10. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 7 to 9, wherein said crystalline form is an anhydrate.

11. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 7 to 10, obtainable by:

a) mixing 10 mg of COMPOUND in crystalline form 1 in 0.05 mL acetonitrile;

b) stirring in a closed 4 mL vial for up to three days;

c) isolating; and drying at reduced pressure and room temperature for 2 hours.

12. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11, for use as a medicament.

13. A pharmaceutical composition comprising as active ingredient a crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11, and at least one pharmaceutically acceptable carrier.

14. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11, for use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone, and at least one pharmaceutically acceptable carrier material.

15. A crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11, or a pharmaceutical composition according to claim 13 for use in the treatment or prevention of a disease or disorder selected from the group consisting of sleep disorders selected from the group consisting of dyssomnias, parasomnias, sleep disorders associated with a general medical condition and substance-induced sleep disorders; anxiety disorders; and addiction disorders.

16. Use of a crystalline form of the compound (S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11 for the preparation of a medicament for the treatment or prevention of a disease or disorder selected from the group consisting of sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, and appetite disorders.

17. A method of treatment or prophylaxis of sleep disorders, anxiety disorders, addiction disorders, cognitive dysfunctions, mood disorders, or appetite disorders; comprising administering to a patient an effective amount of a crystalline form of the compound(S)-(2-(6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone according to any one of claims 1 to 11, or of a pharmaceutical composition according to claim 13.

Figure 1

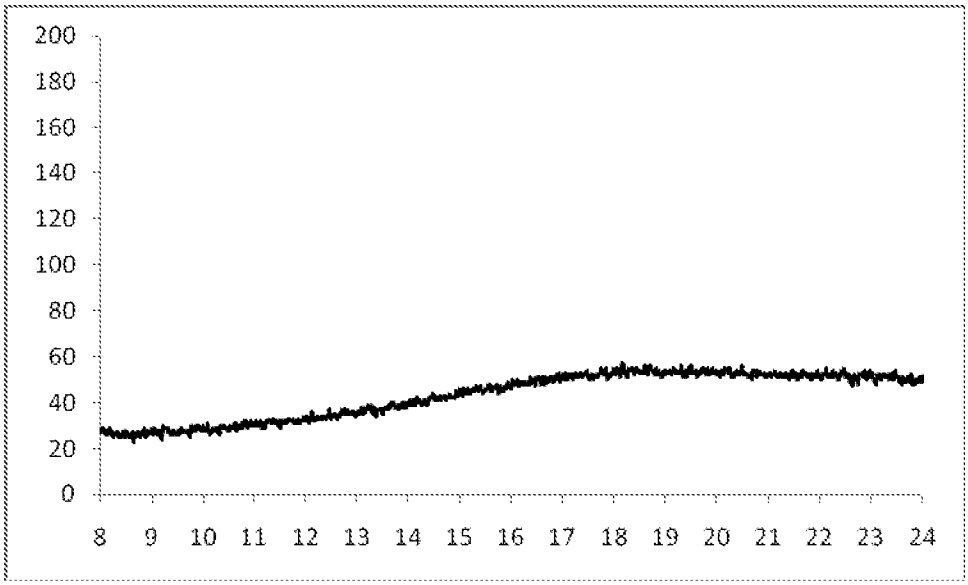


Figure 2

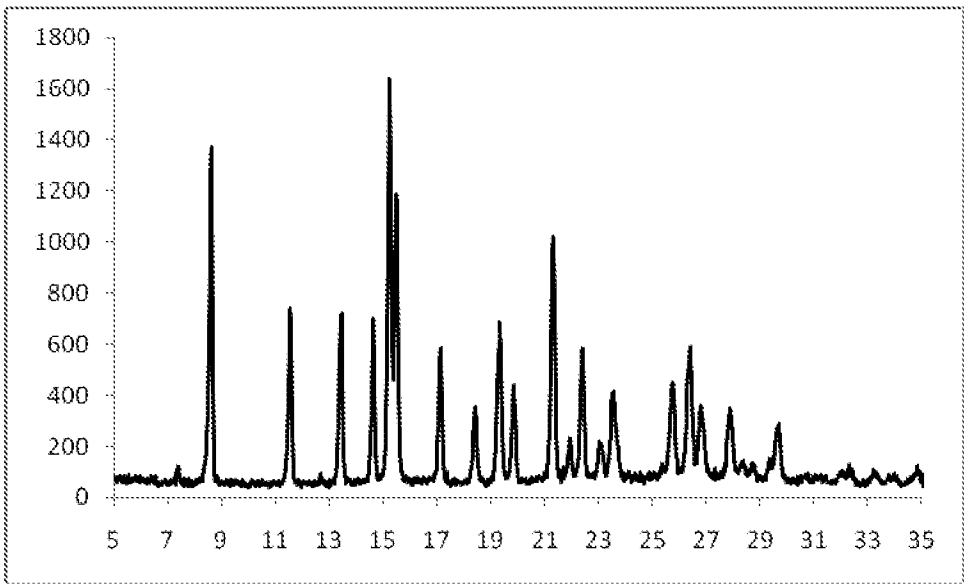


Figure 3

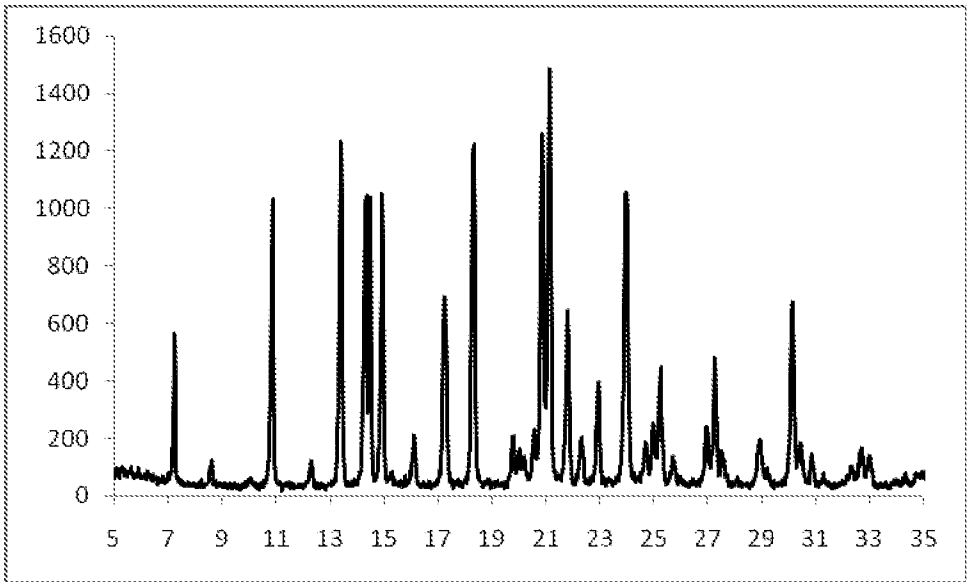


Figure 4

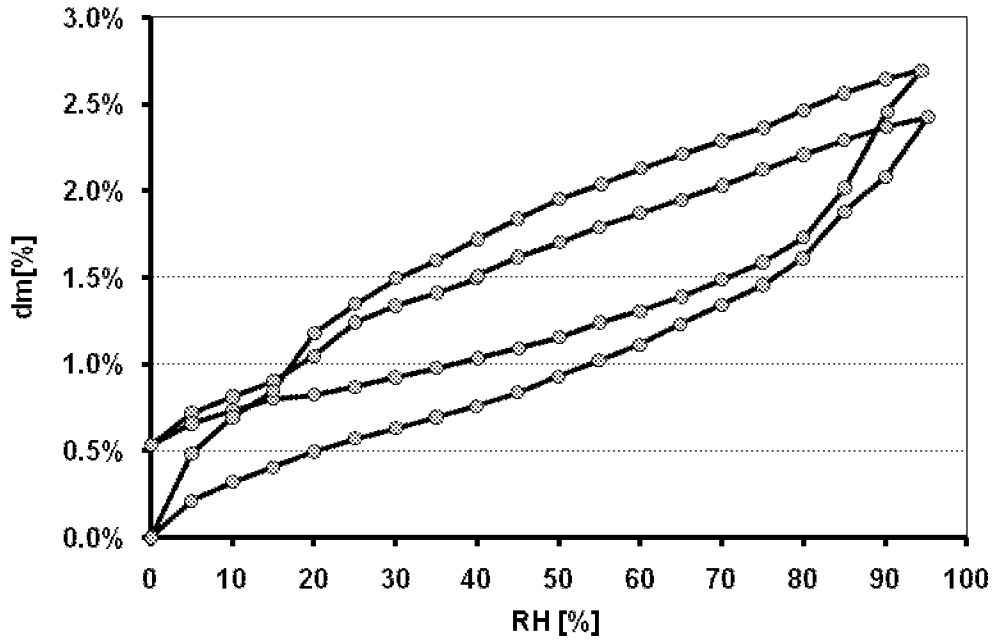


Figure 5

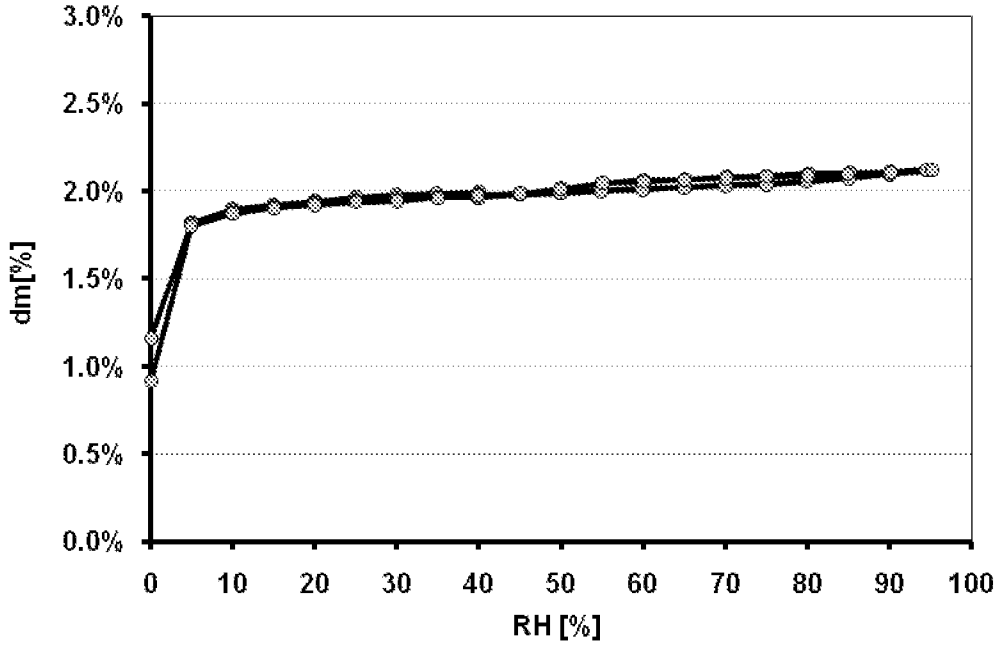
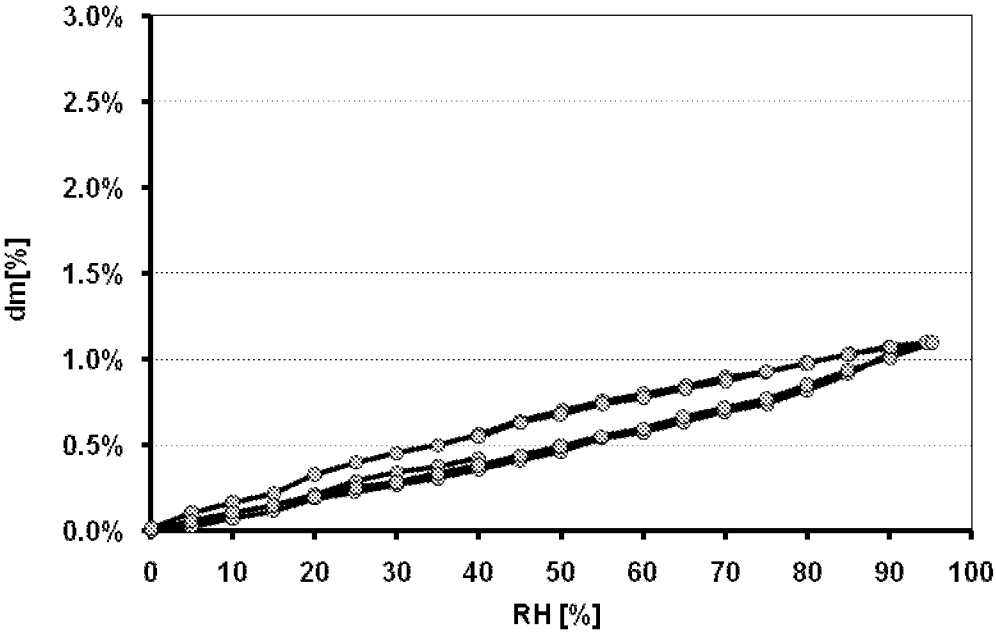


Figure 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/066508

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/4192 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/182972 A1 (ACTELION PHARMACEUTICALS LTD [CH]) 12 December 2013 (2013-12-12) page 143; example 5.36 claims	1-17
A	WO 2010/072722 A1 (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; AMANTINI DAVID [IT]) 1 July 2010 (2010-07-01) examples claims	1-17
A	WO 03/002561 A1 (SMITHKLINE BEECHAM PLC [GB]; BRANCH CLIVE LESLIE [GB]; CHAN WAI NGOR [] 9 January 2003 (2003-01-09) cited in the application examples claims	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2015	16/02/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stix-Malaun, Elke

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/066508

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