

A GABA receptor modulator for treating disorders associated with sleep spindle deficits

5 Technical field

The present invention relates to the use of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or pharmaceutically acceptable salts thereof, which is a known GABA receptor modulator, for use in enhancing sleep spindles, and for use in the treatment of diseases and disorders associated with sleep spindle deficits.

Background

Sleep spindle oscillations are characteristic transient features of the sleep electroencephalogram (EEG) of sleeping mammals, with well recognizable, burst like sequence of 10–15 Hz sinusoidal cycles of 0.5-2 s duration during N2 phase of sleep. Sleep spindles hallmark the N2 stage of non-rapid-eye-movement sleep (NREMS) and belong to the most heritable EEG signatures. Higher sleep spindle densities correlate with longer N2 sleep duration and greater resilience to external perturbation. Sleep spindles generate massive Ca²⁺ influx into cortical pyramidal neurons, initiating intracellular cascades involved in generating synaptic plasticity.

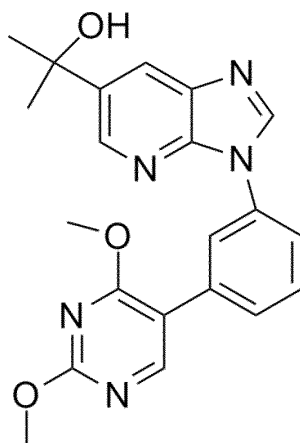
Sleep plays a major role in cognitive functions: Sleep spindle density correlates with markers of intelligence, but also with several disorders leading to cognitive deficits and dementia. Moreover, a number of disease-linked genes are highly enriched in thalamic spindle-generating circuits, including several underlying attentional disorders and schizophrenia (Fernandez and Lüthi, 2020).

Numerous diseases and disorders have been associated with sleep spindle deficit, including *neurodevelopmental diseases or disorders*, *neuropsychiatric diseases or disorders*, and *neurodegenerative diseases or disorders*. Thus, there is a need for effective methods allowing for modulation and enhancement of sleep spindles.

Summary

This invention concerns methods for modulation and enhancement of sleep spindles, useful in treating disease or disorders associated with a sleep spindle deficit. The

present inventors have surprisingly found that 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol, Compound **1**, which is a known GABA_A receptor modulator, has sleep spindle-enhancing activity.

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Thus, in a major aspect, the present invention concerns compound **1**, for use in the treatment of a disease or disorder associated with a sleep spindle deficit. In particular, compound **1** may be included in treatments of neurodevelopmental disease or disorder.

In one aspect, the current invention relates to a method for treating a disease or disorder associated with a sleep spindle deficit, the method comprising administering Compound **1**, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In one aspect, the present invention relates to use of Compound **1**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of a disease or disorder associated with a sleep spindle deficit.

In one aspect, the present invention relates to a method of increasing the number, frequency, power, or duration of sleep spindles in a subject, the method comprising administration of Compound **1**, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In one aspect, the present invention concerns compound **1** for use in enhancing sleep spindles in a subject suffering from:

- a) a neurodevelopmental disease or disorder, such as Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD),
5 Developmental language disorder (DLD), Intellectual disabilities (IDs),
Intellectual development disorder (IDD), Global developmental delay (GDD),
Motor disorders including developmental coordination disorder,
Neurogenetic disorders, Angelman syndrome and/or learning disorder;
- b) a neuropsychiatric disease or disorder, such as schizophrenia, a
10 schizoaffective disorder, a bipolar disorder, a schizotypal personality
disorder, anxiety and/or depression; and/or
- c) a neurodegenerative disease or disorder, such as Alzheimer's disease,
dementia, and/or Parkinson's disease.

15 In one aspect, the present invention concerns compound **1** for use in the treatment or prevention of a disease or disorder selected from:

- a) neurodevelopmental disease or disorder, such as Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD),
20 Developmental language disorder (DLD), Intellectual disabilities (IDs),
Intellectual development disorder (IDD), Global developmental delay (GDD),
Motor disorders including developmental coordination disorder,
Neurogenetic disorders, Angelman syndrome and/or learning disorder;
- b) a neuropsychiatric disease or disorder such as schizophrenia, a
25 schizoaffective disorder, a bipolar disorder, a schizotypal personality
disorder, anxiety and/or depression; and/or
- c) a neurodegenerative disease or disorder, such as Alzheimer's disease,
dementia, and/or Parkinson's disease.

30 Description of Drawings

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Figure 1. Compound **1** significantly increases sleep spindles.

Each graph shows the effect (normalized to the pre-injection period) of systemic administration of 10 mg/kg Compound **1** on the indicated sleep spindle parameters, respectively **A.** Number of spindles pr minute, **B.** Spindle frequency, **C.** Spindle power
35 and **D.** Spindle duration, during natural sleep in normal Wistar rats (injection time is

indicated by the dashed line). Each data point is the average for the 20 min bin.

* $p < 0.05$; ** $p < 0.01$.

Detailed description

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The present disclosure is based, at least in part, on the finding that administration of Compound 1 provides increases in sleep spindles, such as increased number of sleep spindles and increased duration of sleep spindles. Accordingly, the present disclosure provides methods for treating a subject having a disorder associated with a sleep spindle deficit using an effective amount of Compound 1.

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Biological activity

Compound 1 of the present invention is capable of modulation the GABA_A receptor complex, and is a proven positive allosteric modulator (PAM) of GABA_A receptors.

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Compound 1 is selective for GABA_A receptors containing the α_3 subunit and to a minor extent, α_2 and α_5 subunits. Compound 1 is demonstrated herein to increase number of sleep spindles, and moreover increase spindle frequency, spindle power and spindle duration.

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Methods of therapy

Being a ligand for GABA_A receptors, Compound 1 is of use in the treatment, prevention, and/or alleviation of disorders of a living body, including human. In one aspect, the current invention relates to a method for treating a disease or disorder associated with a sleep spindle deficit, the method comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

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In one aspect, the present invention relates to Compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a disease or disorder associated with a sleep spindle deficit.

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In one aspect, the present invention relates to use of Compound 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of a disease or disorder associated with a sleep spindle deficit.

In one embodiment of the present invention, the treatment by Compound 1 is acute.
In one embodiment of the present invention, the treatment by Compound 1 is prophylactic. In one embodiment of the present invention, the treatment by Compound 1 is preventive. In one embodiment of the present invention, the treatment by Compound 1 is ameliorative. In one embodiment of the present invention, the treatment by Compound 1 is symptomatic.

Preferably, the subject is a mammal, such as a human. In some embodiments, the subject is having, is suspected of having, or at risk of developing, a disease or disorder associated with sleep spindle deficit. In some embodiments, the subject is a human subject having, suspected of having, or at risk of developing schizophrenia.

In some embodiments, Compound 1 is administered at a therapeutically effective dose. In some embodiments, the subject is administered a dose of Compound 1, or a pharmaceutically acceptable salt thereof, in the range of 0.001 – 100 mg/kg. In one embodiment of the present invention, the treatment by Compound 1 is administered to a subject as a dose ranging from 0.001 mg/kg – 100 mg/kg, such as 0.001 – 0.01 mg/kg, such as 0.01 – 0.05 mg/kg, such as 0.05 – 1.0 mg/kg, such as 1 – 5mg/kg, such as 5 – 10 mg/kg, such as 10 – 25 mg/kg, such as 25 – 50 mg/kg, such as 50 – 100 mg/kg.

In some embodiments, Compound 1 is administrated by the peroral route.

In one embodiment, compound 1 is administered in combination with one or more additional therapeutically active ingredients.

In one aspect, the present invention relates to a method of modulating or enhancing sleep spindles in a subject, the method comprising administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the number of sleep spindles is increased. In some embodiments, the frequency of sleep spindles is increased. In some embodiments, the power of sleep spindles is increased. In some embodiments, the duration of sleep spindles is increased.

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In one aspect, the present invention relates to a method of increasing the number, frequency, power, or duration of sleep spindles in a subject, the method comprising administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, said subject suffers from a disease or disorder associated with a sleep spindle deficit. In some embodiments, said disease or disorder associated with a sleep spindle deficit is as defined herein.

Diseases and disorders associated with a sleep spindle deficit

Numerous diseases and disorders have been associated with sleep spindle deficit, including *neurodevelopmental diseases or disorders, neuropsychiatric diseases or disorders, neurodegenerative diseases or disorders, and pain*. Such diseases and disorders can be treated according to the present invention by administration of Compound 1.

Neurodevelopmental diseases or disorders

Neurodevelopmental disorders are a group of neurological disorders that affect the development of the nervous system, leading to abnormal brain function which may affect emotion, learning ability, self-control, and memory.

Examples of neurodevelopmental disorders include:

- Attention deficit hyperactivity disorder (ADHD)
- Developmental language disorder (DLD) (formerly known as SLI- Specific Language Impairment)
- Communication, speech, or language disorders, expressive language disorder, fluency disorder, social (pragmatic) communication disorder, and speech sound disorder.
- Autism spectrum disorder (ASD)
- Intellectual disabilities (IDs) or intellectual development disorder (IDD), (previously called mental retardation) and global developmental delay (GDD)
- Angelman Syndrome
- Motor disorders including developmental coordination disorder, stereotypic movement disorder, and tic disorders (such as Tourette's syndrome), and CAS - Apraxia of speech.

- Neurogenetic disorders, such as Fragile X syndrome, Down syndrome, Rett syndrome, hypogonadotropic hypogonadal syndromes
- Specific learning disorders, like dyslexia, including acquired dyslexia and developmental dyslexia, or dyscalculia.
- 5 – Traumatic brain injury and disorders due to neurotoxicants, and behavioral disorders including conduct disorder etc. caused by heavy metals, such as mercury, lead, chromium, platinum etc., hydrocarbons like dioxin, PBDEs and PCBs, medications and drugs, and others.
- 10 – Fetal Alcohol Spectrum Disorders (FASD) can exhibit a combination of the above, most commonly ADHD, because of this, FASD is usually under-diagnosed, yet it is estimated that about 1 in 20 people may be affected.

A link between sleep spindles and attention disorders, such as in autism-spectrum disorders or attention-deficit hyperactivity disorders has been identified. Moreover a link
15 between the gene *PTCHD1* (Patched domain-containing protein 1) that leads to broad intellectual disabilities in humans when mutated and sleep spindle deficits (Fernandez and Lüthu, 2020).

In some embodiments, the disease or disorder associated with a sleep spindle deficit is
20 a neurodevelopmental disease or disorder. In some embodiments, the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination
25 disorder, Neurogenetic disorders, or learning disorders. In some embodiments the learning disorder is dyslexia, such as acquired dyslexia or developmental dyslexia. In some embodiments, the neurodevelopmental disease or disorder is Angelman Syndrome.

30 In one aspect, the present invention relates to Compound 1 for use in enhancing sleep spindles in a subject suffering from a neurodevelopmental disease or disorder. In one aspect, the present invention relates to Compound 1 for use in enhancing sleep spindles in a subject suffering from a neurodevelopmental disease or disorder selected
35 from Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual

development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and learning disorder, or a combination thereof.

5 In aspect, the present invention relates to Compound 1 for use in the treatment or prevention of a neurodevelopmental disease or disorder. In aspect, the present invention relates to Compound 1 for use in the treatment or prevention of Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development
10 disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and/or learning disorder, or a combination thereof.

Neuropsychiatric diseases or disorders

15 Neuropsychiatric diseases or disorders encompasses a broad range of conditions, that involve both neurology and psychiatry. Examples include schizophrenia, schizoaffective disorders, such as schizoaffective depressive and schizoaffective manic disorders, bipolar disorders such as type I and type II bipolar disorder (Petit et al., 2022), anxiety and depression. The key component of neuropsychiatric disorders is
20 that the symptoms tend to impact brain function, emotion and mood.

Studies on deficits in sleep spindles have accumulated for schizophrenia. The link between sleep spindle deficit and schizophrenia is well established. In schizophrenia patients a decreased spindle density in N2 or whole NREMS is a
25 consistent common denominator across patient categories ranging from early-stage psychosis to chronically medicated groups. In chronically medicated schizophrenia, there are observations on decreased ipsilateral coherence and on changes in sleep spindle amplitude and duration (Fernandez and Lüthi, 2020). Moreover a trend for decreased sleep spindle density in first-degree relatives is also reported, independently
30 of whether or not these suffered from neuropsychiatric symptoms, highlighting the importance of understanding genetic risk factors (Fernandez and Lüthi, 2020).

Genes associated with neuropsychiatric disorders have been identified. An example is the third member of the T-type channel family, $Ca_v3.3$ encoded by *CACNA1I*, which
35 has been identified as genetic risk factor in schizophrenia (Ghaleb et al., 2021).

In some embodiments, the disease or disorder associated with a sleep spindle deficit to be treated by Compound 1 is a neuropsychiatric disease or disorder. In some
5 embodiments, the neuropsychiatric disease or disorder is schizophrenia. In some
embodiments, the schizophrenia is selected from the group consisting of paranoid
schizophrenia, disorganized schizophrenia, catatonic schizophrenia, childhood
schizophrenia, and schizoaffective disorder.

10 In some embodiments, the neuropsychiatric disease or disorder is a schizoaffective
disorders. In some embodiments, the schizoaffective disorder is a schizoaffective
depressive or schizoaffective manic disorder.

15 In some embodiments, the neuropsychiatric disease or disorder is bipolar disorder. In
some embodiments, the bipolar disorders is type I or type II bipolar disorder.

 In some embodiments, the neuropsychiatric disease or disorder is a schizotypal
personality disorder.

20 In some embodiments, the neuropsychiatric disease or disorder is anxiety. In some
embodiments, the anxiety is associated with pain. In some embodiments, the anxiety is
caused by pain.

25 In some embodiments, the neuropsychiatric disease or disorder is depression. In some
embodiments, the depression is associated with pain. In some embodiments, the
depression is caused by pain. In some embodiments the depression is major
depression, or treatment-resistant depression. In some embodiments the depression is
treatment-resistant major depression.

30 In one aspect, the present invention relates to Compound 1 for use in enhancing sleep
spindles in a subject suffering from a neuropsychiatric disease or disorder. In one
aspect, the present invention relates to Compound 1 for use in enhancing sleep
spindles in a subject suffering from a neuropsychiatric disease or disorder selected
from schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal
personality disorder, anxiety and depression, or a combination thereof.

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In one aspect, the present invention relates to Compound 1 for use in the treatment or prevention of a neuropsychiatric disease or disorder. In one aspect, the present invention relates to Compound 1 for use in the treatment or prevention of a neuropsychiatric disease or disorder selected from schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal personality disorder, anxiety and depression, or a combination thereof.

Neurodegenerative diseases or disorders

Neurodegenerative diseases or disorders, including age-related neurodegenerative diseases are characterized by exacerbated cognitive decline and sleep disturbances compared with healthy ageing (Fernandez and Lüthi, 2020). Examples of neurodegenerative disorders includes dementia, Alzheimer's disease, and Parkinson's disease. Patients suffering from neurodegenerative disorders have a diversity of structural and functional alterations in brain stem, thalamus, and cortex.

Reduction of sleep spindle and sleep spindle density are observed in Alzheimer's patients, Alzheimer's patients with dementia as well as Parkinson's disease patients and people suffering from Mulvihill-Smith syndrome (Fernandez and Lüthi, 2020).

Because sleep spindles are reduced in these diseases, they can be treated according to the present invention. In some embodiments, the disease or disorder associated with a sleep spindle deficit is a neurodegenerative disease or disorder. In some embodiments, the neurodegenerative disease or disorder is Alzheimer's disease, dementia, and/or Parkinson's disease.

In one aspect, the present invention relates to Compound 1 for use in enhancing sleep spindles in a subject suffering from a neurodegenerative disease or disorder. In one aspect, the present invention relates to Compound 1 for use in enhancing sleep spindles in a subject suffering from a neurodegenerative disease or disorder selected from Alzheimer's disease, dementia, and Parkinson's disease, or a combination thereof.

In one aspect, the present invention relates to Compound 1 for use in the treatment or prevention of a neurodegenerative disease or disorder. In one aspect, the present invention relates to Compound 1 for use in the treatment or prevention of a

neurodegenerative disease or disorder selected from Alzheimer's disease, dementia, and Parkinson's disease, or a combination thereof.

Pain

5 Sleep spindle density is decreased in the chronic pain state, indicating a close relationship between sleep spindle density and persistent pain. Studies have shown that chronic pain is associated with poor sleep quality, especially interruptions in slow wave, NREM sleep. Moreover, poor quality sleep has been shown to be a risk factor for chronic pain, with numerous studies implicating sleep in pain-associated depression and anxiety.

10 It has recently been demonstrated that acoustic stimulation, pink noise, can enhance sleep spindles and relieve chronic pain symptoms (Caravan et al., 2019).

In some embodiments, the disease or disorder associated with a sleep spindle deficit is pain. As explained, sleep spindles may be decreased in subjects suffering from pain. In some embodiments, the pain is chronic pain. In some embodiments, the pain is inflammatory pain, nociceptive pain, or neuropathic pain. In some embodiments, the pain further leads to pain-associated depression and/or pain-associated anxiety.

20 ***Identification of subjects having, or at risk of developing a disease or disorder associated with sleep spindle deficit***

Methods described herein encompass detecting a sleep spindle deficit. In some embodiments, a sleep spindle deficit comprises a deficit, relative to a control, in any aspect of a sleep spindle, of at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 25 90%, 100%, or at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100- fold. In some embodiments, a sleep spindle deficit comprises a deficit in at least one aspect of a sleep spindle. In some embodiments, a sleep spindle deficit comprises a deficit in at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten aspects of a sleep 30 spindle. In some embodiments, a sleep spindle deficit comprises a deficit in more than one aspect of a sleep spindle.

Methods described herein encompass detecting characteristics of sleep spindles by any technique or method known in the art. In some embodiments, detecting a 35 characteristic of a sleep spindle comprises detection via electroencephalogram (EEG)

or via electrocardiogram (ECG). It should be appreciated that any method known to one of ordinary skill in the art for detecting sleep spindles can be compatible with aspects of the disclosure.

5 For example, methods can comprise: detecting sleep spindle density; detecting sleep spindle duration; detecting sleep spindle amplitude; detecting sleep spindle frequency, detecting the number of oscillations of a sleep spindle; and/or detecting spindle symmetry.

10 For example, characteristics of sleep spindles may be detected in a subject to whom a treatment is administered, before and after the treatment and/or during the course of the treatment. For example, in some embodiments, if a characteristic of sleep spindles improves during the course of treatment, then this may be an indication that the treatment is effective and should be continued.

15 In some embodiments, the method of the present invention further comprises a step of determining that a subject has, is suspected of having, or is at risk of developing a disorder associated with a sleep spindle deficit. In some embodiments, said step comprises detecting sleep spindles with a method known to one of ordinary skill in the art for detecting sleep spindles, such as an electroencephalogram (EEG).

In some embodiments, the step of determining that a subject has, is suspected of having, or is at risk of developing a disorder associated with a sleep spindle deficit comprises determining whether the subject has a gene mutation associated with sleep spindle deficit, such as a mutation in the gene PTCHD1, or the gene encoding the CACNA1I protein.

25 In some embodiments, the subject is a human subject having, suspected of having, or at risk of developing a schizophrenia disorder. In some embodiments, the subject is a human subject having a mutation in the gene encoding the CACNA1I protein.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration, including pharmaceutically (i.e. physiologically) acceptable salts. Examples of pharmaceutically acceptable addition salts include, without

limitation, non-toxic inorganic and organic acid addition salts such as hydrochloride, hydrobromide, nitrate, perchlorate, phosphate, sulphate, formate, acetate, aconate, ascorbate, benzenesulphonate, benzoate, cinnamate, citrate, embonate, enantate, fumarate, glutamate, glycolate, lactate, maleate, malonate, mandelate, methanesulphonate, naphthalene-2-sulphonate, phthalate, salicylate, sorbate, stearate, succinate, tartrate, toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art. Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of compound **1** of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of compound **1** of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art. In the context of this invention the "onium salts" of *N*-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Labelled Compounds

The chemical compound of the present invention may be used in its labelled or unlabelled form. In the context of this invention the labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for in vivo receptor imaging. The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I , and ^{18}F .

The physical method for detecting the labelled isomer of the present invention may be

selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

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Pharmaceutical compositions

The invention also provides use of pharmaceutical compositions comprising therapeutically effective amount of compound 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or
10 diluent.

While compound 1 of the present invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a
15 pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, and,
20 optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof. Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonary, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral
25 (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of
30 sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

Compound 1 of the invention, together with a conventional adjuvant, carrier, or diluent,
35 may thus be placed into the form of pharmaceutical compositions and unit dosages

thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Compound 1 of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from Compound 1 of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In one embodiment of the present invention, Compound 1, or the pharmaceutically acceptable salt thereof, is the only active pharmaceutical ingredient. In one embodiment of the present invention, Compound 1 is within a pharmaceutical composition, wherein the composition comprises one or more adjuvants, excipients, carriers, buffers, diluents, and/or other pharmaceutical auxiliaries. In one embodiment of the present invention, the pharmaceutical composition consists of Compound 1, or the pharmaceutically acceptable salt thereof, and one or more adjuvants, excipients, carriers, buffers, diluents, and/or other pharmaceutical auxiliaries.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet,

cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

5 A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED₅₀, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by ratio between plasma levels resulting in therapeutic effects and plasma ratios resulting in toxic effects. Pharmaceutical
10 compositions exhibiting large therapeutic indexes are preferred.

The dose administered may be adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage can be determined by the
15 practitioner.

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired
20 therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 10.000 mg of active ingredient per individual dose, preferably of from about 1 to about 1000 mg, most preferred of from about 10 to about 500 mg, are suitable for therapeutic treatments. The active ingredient may be administered in one or several doses per day. A satisfactory result may, in
25 certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

30 **Definitions**

The term "*sleep spindles*" as used herein refers to bursts of oscillatory brain activity generated in the reticular nucleus of the thalamus that occur during sleep. In some embodiments, sleep spindles comprise a burst of 12-15 Hz. In some embodiments, sleep spindles occur during stage 2 non-rapid eye movement (NREM) sleep (N2).

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The term "*sleep spindle deficit*" as used herein refers to a deficit in any aspect of a sleep spindle, including, but not limited to, number of spindles, spindle density, spindle amplitude, spindle duration, spindle peak frequency, and spindle sigma power.

5 The term "*disease disorder associated with a sleep spindle deficit*," as used herein, refers to any disorder associated with a deficit in a subject's sleep spindles or a deficit in one or more characteristics associated with a subject's sleep spindles. Characteristics of sleep spindles include but are not limited to: the total number of sleep spindle oscillations throughout the NREM sleep, sleep spindle density (e.g.,
10 number of sleep spindles per minute during sleep), sleep spindle duration, sleep spindle amplitude, sleep spindle frequency power, sleep spindle frequency, sleep spindle power, sleep spindle integrated power, sleep spindle morphology, spindle symmetry, and sleep spindle coherence with slow wave oscillations. Sleep spindle deficits include, but are not limited to, deviation in one or more of these characteristics
15 from a population mean by more than 0.5 standard deviation (SD), 1 SD, or 2 SD. In some embodiments, sleep spindle deficits include, but are not limited to, deviation in one or more of these characteristics from a close relative by more than 0.5 SD, 1 SD, or 2 SD. Examples of disorders associated with a sleep spindle deficit include, but are not limited to, bipolar disorder, intellectual disability, schizophrenia disorders, epilepsy,
20 and autism spectrum disorders.

In some embodiments, disorders associated with a sleep spindle deficit are schizophrenia disorders. Schizophrenia disorders include, but are not limited to, paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia,
25 childhood schizophrenia, and schizoaffective disorder. It should be appreciated that any disorder associated with a sleep spindle deficit, including any schizophrenia disorder, is encompassed by aspects of the disclosure.

The term "*preventive treatment*," as used herein to describe the present invention,
30 means that the compound, pharmaceutical composition or combination is administered to a subject to inhibit or stop or reduce the risk of the relevant condition or symptom of said condition from occurring in a subject.

The term "*prophylactic treatment*" as used herein to describe the present invention,
35 refers to the treatment of subjects having, or at risk of having a specified condition or

symptom of the condition, but not presently having or experiencing the symptoms of the condition.

5 The term "*ameliorative treatment*" as used herein to describe the present invention, refers to the treatment of subjects having, or at risk of having a specified symptom, wherein the subjects are presently having or experiencing the symptoms of the condition.

10 The term "*symptomatic treatment*" as used herein to describe the present invention, refers to ameliorating a specified condition or disorder or symptoms accompanied therewith to a significant extent.

Items

- 15 1. A method for treating a disease or disorder associated with a sleep spindle deficit, the method comprising administering to a subject in need thereof 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 20 2. The method according to item 1, wherein the wherein the disease or disorder associated with a sleep spindle deficit is a neurodevelopmental disease or disorder.
- 25 3. The method according to item 2, wherein the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, or learning disorders.
- 30 4. The method according to item 2, wherein the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Angelman syndrome, Motor disorders including developmental
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coordination disorder, Neurogenetic disorders, or learning disorders, such as acquired dyslexia, developmental dyslexia, or dyscalculia.

- 5 5. The method according to item 1, wherein the disease or disorder associated with a sleep spindle deficit is a neuropsychiatric disease or disorder.
- 10 6. The method according to item 5, wherein the neuropsychiatric disease or disorder is schizophrenia, a schizoaffective disorder, a bipolar disorder, and/or a schizotypal personality disorder.
- 15 7. The method according to item 6, wherein the schizoaffective disorder is a schizoaffective depressive disorder or a schizoaffective manic disorder.
8. The method according to item 6, wherein the bipolar disorder is type I or type II bipolar disorder.
- 20 9. The method according to item 6, wherein the schizophrenia is selected from the group consisting of paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, childhood schizophrenia, and schizoaffective disorder.
10. The method according to item 5, wherein the neuropsychiatric disease or disorder is anxiety.
- 25 11. The method according to item 10, wherein the anxiety is associated with pain.
12. The method according to item 10, wherein the anxiety is caused by pain.
- 30 13. The method according to item 5, wherein the neuropsychiatric disease or disorder is depression.
14. The method according to item 13, wherein the depression is associated with pain.
- 35 15. The method according to item 13, wherein the depression is caused by pain

16. The method according to item 13, wherein the depression is major depression, or treatment-resistant depression, such as treatment-resistant major depression.
- 5 17. The method according to item 1, wherein the disease or disorder associated with a sleep spindle deficit is a neurodegenerative disease or disorder.
18. The method according to item 17, wherein the neurodegenerative disease or disorder is Alzheimer's disease, dementia, and/or Parkinson's disease.
- 10 19. The method according to item 1, wherein the disease or disorder associated with a sleep spindle deficit is pain, such as chronic pain.
20. The method according to item 19, wherein the pain is inflammatory pain, nociceptive pain, or neuropathic pain.
- 15 21. The method according to items 19-20, wherein the pain further leads to pain-associated depression and/or pain-associated anxiety.
- 20 22. The method according to any one of the preceding items, wherein the subject is having, is suspected of having, or at risk of developing, a disease or disorder associated with sleep spindle deficit.
23. The method according to any one of the preceding items, wherein the subject is a human subject having, suspected of having, or at risk of developing schizophrenia.
- 25 24. The method according to any one of the preceding items, wherein the method further comprises the step of determining that a subject has, is suspected of having, or is at risk of developing a disorder associated with a sleep spindle deficit comprising detecting sleep spindles with a method known to one of ordinary skill in the art for detecting sleep spindles, such as an electroencephalogram (EEG).
- 30 25. The method according to any one of the preceding items, wherein the method further comprises the step of determining that a subject has, is suspected of
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having, or is at risk of developing a disorder associated with a sleep spindle deficit comprising determining whether the subject has a gene mutation associated with sleep spindle deficit, such as a mutation in the gene PTCHD1, or the gene encoding the CACNA1I protein.

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26. The method according to any one of the preceding items, wherein the subject is administered a dose in the range of 0.001 – 100 mg/kg.

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27. The method according to any one of the preceding items, wherein of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof is administered by the peroral route.

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28. The method according to any one of the preceding items, wherein the treatment is curative, preventive, protective, palliative, prophylactic, symptomatic, and/or ameliorative.

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29. 2-(3-(3-(2,4-Dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a disease or disorder associated with a sleep spindle deficit.

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30. Use of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine-6-yl)propan-2-ol, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of a disease or disorder associated with a sleep spindle deficit.

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31. A method of modulating or enhancing sleep spindles in a subject, the method comprising administration of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.

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32. The method according to item 31, wherein the number of sleep spindles is increased.

33. The method according to item 31, wherein the frequency of sleep spindles is increased.
- 5 34. The method according to item 31, wherein the power of sleep spindles is increased.
35. The method according to item 31, wherein the duration of sleep spindles is increased.
- 10 36. The method according to item 31, wherein the number and duration of sleep spindles are increased, without affecting the frequency and power of the of sleep spindles.
- 15 37. A method for treating a disease or disorder associated with a sleep spindle deficit, wherein the disease or disorder associated with a sleep spindle deficit is a neurodevelopmental disease or disorder, a neuropsychiatric disease or disorder, and/or a neurodegenerative disease or disorder, the method comprising administering to a subject in need thereof 2-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a
20 pharmaceutically acceptable salt thereof.
- 25 38. A method for treating a neurodevelopmental disease or disorder, a neuropsychiatric disease or disorder, and/or a neurodegenerative disease or disorder, the method comprising administering to a subject in need thereof 2-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 30 39. The method according to item 38, wherein the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and/or learning disorder.

40. The method according to item 38, wherein the neuropsychiatric disease or disorder is: schizophrenia, a schizoaffective disorder, a bipolar disorder, and/or a schizotypal personality disorder.
- 5 41. The method according to item 0, wherein schizophrenia is selected from the group consisting of paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, or childhood schizophrenia, wherein the schizoaffective disorder is a schizoaffective depressive disorder or a schizoaffective manic disorder, and wherein the bipolar disorder is type I or type 10 II bipolar disorder.
42. The method according to item 38, wherein the neuropsychiatric disease or disorder is anxiety or depression.
- 15 43. The method according to item 38, wherein the neuropsychiatric disease or disorder is: anxiety associated with pain, anxiety caused by pain, depression associated with pain, depression associated with pain, major depression, and/or treatment-resistant depression.
- 20 44. The method according to item 38, wherein the neurodegenerative disease or disorder is: Alzheimer's disease, dementia, and/or Parkinson's disease.
- 25 45. A method of increasing the number, frequency, power, or duration of sleep spindles in a subject, the method comprising administration of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 30 46. The method of item 0, wherein the subject suffers from a disease or disorder associated with a sleep spindle deficit.
- 35 47. The method according to item 46, wherein the disease or disorder associated with a sleep spindle deficit is a neurodevelopmental disease or disorder.
48. The method according to item 47, wherein the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum

disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, or learning disorders.

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49. The method according to item 46, wherein the disease or disorder associated with a sleep spindle deficit is a neuropsychiatric disease or disorder.

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50. The method according to item 49, wherein the neuropsychiatric disease or disorder is schizophrenia, a schizoaffective disorder, bipolar disorder, and/or a schizotypal personality disorder.

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51. The method according to item 50, wherein the schizoaffective disorder is a schizoaffective depressive or schizoaffective manic disorders.

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52. The method according to item 50, wherein the bipolar disorder is type I or type II bipolar disorder.

53. The method according to item 50, wherein the schizophrenia is selected from the group consisting of paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, childhood schizophrenia, and schizoaffective disorder.

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54. The method according to item 46, wherein the disease or disorder associated with a sleep spindle deficit is a neurodegenerative disease or disorder.

55. The method according to item 54, wherein the disease or disorder associated with a sleep spindle deficit is Alzheimer's disease, dementia, and/or Parkinson's disease.

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56. The method according to item 46, wherein the disease or disorder associated with a sleep spindle deficit is pain, such as chronic pain.

57. The method according to item 56, wherein the pain is inflammatory pain, nociceptive pain, or neuropathic pain.

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58. The method according to any one of items 56 or 57, wherein the pain further leads to pain-associated depression and/or pain-associated anxiety.

59. A compound for use in enhancing sleep spindles in a subject suffering from:

- 5 a) neurodevelopmental disease or disorder, such as Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder,
- 10 Neurogenetic disorders, Angelman syndrome and/or learning disorder;
- b) a neuropsychiatric disease or disorder, such as schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal personality disorder, anxiety and/or depression; and/or
- c) a neurodegenerative disease or disorder such as Alzheimer's disease,
- 15 dementia, and/or Parkinson's disease,
- wherein the compound is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.

20 60. A compound for use in the treatment and/or prevention of a disease or disorder selected from:

- a) a neurodevelopmental disease or disorder, such as Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs),
- 25 Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and/or learning disorder;
- b) a neuropsychiatric disease or disorder, such as schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal personality
- 30 disorder, anxiety and/or depression; and/or
- c) a neurodegenerative disease or disorder, such as Alzheimer's disease, dementia, and/or Parkinson's disease,
- wherein the compound is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt
- 35 thereof.

Examples

Example 1 - Sleep spindle-enhancing activity of Compound 1

5 In this example, the effect of Compound 1 on sleep spindles occurring during natural sleep in normal non-epileptic Wistar rats was investigated.

Materials and methods:

Animals:

10 Male Wistar rats (purchased from Charles River, UK) were provided with normal diet and water *ad libitum*, and kept under a light:dark cycle of 12:12 hours with light on at 7:00 AM. All experimental procedures were performed in accordance with the UK Animals (Scientific Procedures) Act (1986), the European Community Council Directive (2010/63/EU), local ethics committee and expert group guidelines (Lidster et al., 2015).
15 All efforts were made to minimize animal suffering and the number of animals used.

Recording and analysis of sleep spindles of natural sleep

Adult (250-300 g) male Wistar rats were anaesthetized and implanted with EEG electrodes. Additionally the Wistar rats had an electrode positioned in the neck muscle
20 to provide the EMG data required for appropriate classification of sleep stages, as previously described (Roux et al, 2007). Animals were allowed to recover from the surgery for at least five days before any experiment commenced.

For a few days before experiments, Wistar rats were connected to the recording apparatus and placed individually in a Plexiglas box within a Faraday cage for 4-6 hours
25 habituation. On the day of recordings, animals were placed (at 9:00 AM) into the Plexiglas box for 30 minutes (habituation period) followed by 120 min recording (control period) before being injected systemically with either the vehicle 5% DMSO + 0.03% HpbCD (0.03% hydroxypropyl-beta-cyclodextrine) or with Compound 1. They were then recorded for 140 min while being continuously monitored by a researcher. Treatment
30 was assigned in a pseudo-random manner with a cross-over design: each animal received a maximum of two injections separated by at least five days.

The EEG signal was acquired through a 4-channels differential pre-amplifier (high-pass filter 0.1 Hz, SuperTech, Hungary) connected to a 4-channel BioAmp amplifier (1000 gain, low-pass filter 500 Hz, SuperTech, Hungary) and digitized at 1000 Hz using a CED
35 Mk3 1401 (Cambridge Electronic Design, UK). The EEG signal was convolved with

complex Morlet wavelets of 2.5 cycles at a frequency resolution of 0.1 Hz (Kronland-Martin et al., 1987). Using a wavelet ridge extraction method, each oscillatory epoch of the EEG was extracted with an energy threshold to detect its beginning and end (Roux et al., 2007, Garcia S. and Fourcaud-Trocme, N. 2009). The boundary frequencies of wave detection were chosen as from 6 to 14 Hz for spindle oscillations. The threshold was defined as 3 times the average energy during a non-REM sleep period during the control session. Spindle waves with less than 3 cycles were discarded.

Statistical analysis was performed using GraphPad Prism version 9.0 (GraphPad Software, San Diego, USA). Normality of the data was verified with QQ plot. The effect of Compound 1 was assessed by Student's t test for each time bin (20 min). All quantitative data in the text and figures are reported as mean $\pm$ SEM, unless stated otherwise.

Results:

15

Sleep spindles

As shown in Figure 1, the systemic injection of 10 mg/kg Compound 1 significantly enhanced sleep spindles recorded during natural sleep in Wistar rats as indicated by an increase in the number of spindles, which was statistically significant from 100 till 140 min after injection (Figure 1A). A statistically significant increase in spindle frequency (Figure 1B) and power (Figure 1C) was present at 60 and 140 min after injection, respectively. Moreover, an increase in the average spindle duration (Figure 1D) was observed at 80 and 140 min post-injection.

25 Conclusions

Sleep spindles-enhancing activity of Compound 1 .

The data obtained during natural sleep in Wistar rats suggest that Compound 1 is capable of increasing sleep spindle activity, including number of spindles, spindle frequency, spindle power and spindle duration. There is an increased number of spindles at earlier times (60 and 80 min) following injection, but this is not significant due to the large SEM of the available data. At late times (>100 min), the increase is significant.

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Claims

- 5 1. A compound for use in the treatment or prevention of a disease or disorder associated with a sleep spindle deficit, wherein the disease or disorder is selected from: a neurodevelopmental disease or disorder, a neuropsychiatric disease or disorder, and/or a neurodegenerative disease or disorder, and wherein the compound is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 10 2. The compound for use according to claim 1, wherein the disease or disorder associated with a sleep spindle deficit is a neurodevelopmental disease or disorder.
- 15 3. The compound for use according to claim 1 or 2, wherein the neurodevelopmental disease or disorder is Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and/or learning disorder.
- 20 4. The compound for use according to claim 1, wherein the disease or disorder associated with a sleep spindle deficit is a neuropsychiatric disease or disorder.
- 25 5. The compound for use according to claim 1 or 4, wherein the neuropsychiatric disease or disorder is schizophrenia, a schizoaffective disorder, a bipolar disorder, and/or a schizotypal personality disorder.
- 30 6. The compound for use according to claim 1 or 4, wherein the neuropsychiatric disease or disorder is anxiety.
- 35 7. The compound for use according to claim 6, wherein the anxiety is caused by pain.

8. The compound for use according to claim 1 or 4, wherein the neuropsychiatric disease or disorder is depression.
- 5 9. The compound for use according to claim 8, wherein the depression is caused by pain.
- 10 10. The compound for use according to claim 5, wherein the schizophrenia is selected from the group consisting of paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, or childhood schizophrenia, wherein the schizoaffective disorder is a schizoaffective depressive disorder or a schizoaffective manic disorder, and wherein the bipolar disorder is type I or type II bipolar disorder.
- 15 11. The compound for use according to claim 1, wherein the disease or disorder associated with a sleep spindle deficit is a neurodegenerative disease or disorder.
- 20 12. The compound for use according to claim 1 or 11, wherein the neurodegenerative disease or disorder is Alzheimer's disease, dementia, and/or Parkinson's disease.
- 25 13. The compound for use according to any one of the preceding claims, wherein the subject is having, is suspected of having, or at risk of developing, a disease or disorder associated with sleep spindle deficit.
- 30 14. The compound for use according to any one of the preceding claims, wherein the subject is administered a dose in the range of 0.001 – 100 mg/kg.
- 35 15. The compound for use according to any one of the preceding claims, wherein of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof is administered by the peroral route.

16. The compound for use according to any one of the preceding claims, wherein the treatment is curative, preventive, protective, palliative, prophylactic, symptomatic, and/or ameliorative.
- 5 17. 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof, for use in a method of modulating or enhancing sleep spindles in a subject.
- 10 18. 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof, for use in a method of increasing the number, frequency, power, or duration of sleep spindles in a subject.
- 15 19. A compound for use in enhancing sleep spindles in a subject suffering from:
- 20 a) a neurodevelopmental disease or disorder selected from Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and learning disorder, or a combination thereof;
- 25 b) a neuropsychiatric disease or disorder selected from schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal personality disorder, anxiety and depression, or a combination thereof; and/or
- 30 c) a neurodegenerative disease or disorder selected from Alzheimer's disease, dementia, and Parkinson's disease, or a combination thereof, wherein the compound is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 35 20. A method for modulating or enhancing sleep spindle, comprising administration of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

21. A method for increasing the number, frequency, power, and/or duration of sleep spindles, comprising administration of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.
- 5
22. A method for treatment or prevention of a disease or disorder associated with a sleep spindle deficit, wherein the disease or disorder is selected from: a neurodevelopmental disease or disorder, a neuropsychiatric disease or disorder, and/or a neurodegenerative disease or disorder, said method comprising administration of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
- 10
23. Use of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a disease or disorder associated with a sleep spindle deficit, wherein the disease or disorder is selected from: a neurodevelopmental disease or disorder, a neuropsychiatric disease or disorder, and/or a neurodegenerative disease or disorder.
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- 20
24. A compound for use in the treatment or prevention of a disease or disorder selected from:
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- 30
- 35
- a) a neurodevelopmental disease or disorder selected from Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), Developmental language disorder (DLD), Intellectual disabilities (IDs), Intellectual development disorder (IDD), Global developmental delay (GDD), Motor disorders including developmental coordination disorder, Neurogenetic disorders, Angelman syndrome and learning disorder, or a combination thereof;
 - b) a neuropsychiatric disease or disorder selected from schizophrenia, a schizoaffective disorder, a bipolar disorder, a schizotypal personality disorder, anxiety and depression, or a combination thereof; and/or
 - c) a neurodegenerative disease or disorder selected from Alzheimer's disease, dementia, and Parkinson's disease, or a combination thereof,

wherein the compound is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol or a pharmaceutically acceptable salt thereof.