

A GABA receptor modulator for use in the treatment of absence seizures

Technical field

5 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 treating and/or preventing absence seizures.

Background

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Absence seizures

Absence seizure is the term for a type of seizure involving staring spells. This type of seizure is a brief (usually less than 15 seconds) disturbance of brain function due to abnormal electrical activity in the brain. Seizures result from overactivity in the brain.

15 Absence seizures occur most often in people under age 21, usually in children ages 4 to 12.

A generalized absence seizure (non-motor seizure) is a type of dialeptic seizure that is of electrographically generalized onset. It is a generalized seizure characterised by an interruption of activities, a blank stare, and usually the person will be unresponsive when spoken to, which may be mistaken for a brief lapse in attention. The seizure lasts about 10 seconds, though it may last as long as 30 seconds. Typically there's no confusion, headache or drowsiness after the seizure.

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25 Symptoms of absence seizures include:

- A sudden stop in activity without falling.
- Lip smacking.
- Eyelid flutters.
- Chewing motions.
- 30 • Finger rubbing.
- Small movements of both hands.

Afterward, there's usually no memory of the incident. But if the seizure is longer, the person may be aware of missed time. Some people have many episodes daily. When it happens, it can interfere with school or daily activities.

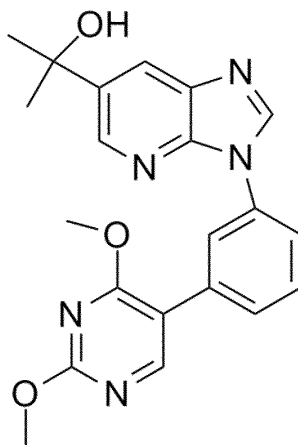
- 5 Absence seizures usually occur in children between ages 4 to 14. A child may have 10, 50, or even 100 absence seizures in a given day and they may go unnoticed.

10 The electrographic EEG signature of absence seizures is 2-4 Hz spike-and-wave discharges. Several epilepsy disorders have been characterized by the occurrence of spike-and-wave discharges and absence seizures. Thus, there is a need for effective methods allowing for modulation of spike-and-wave discharges and absence seizures.

Summary

- 15 This invention concerns methods for treating and preventing absence epilepsy and absence seizures. 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 modulating effects on spike-and-wave discharges and absence seizure activity.

20 Thus, in a major aspect, the present invention concerns compound 1, which is 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol (depicted in formula 1) for use in the treatment and/or prevention of absence seizures.



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In particular, compound 1 may be included in treatments of an epileptic disease or disorder, such as electrical status epilepticus during slow-wave sleep (ESES), Developmental/Epileptic Encephalopathy with Spike Wave Activation In Sleep (DEE-SWAS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile
5 myoclonic epilepsy, Lennox-Gastaut, Dravet Syndrome or Idiopathic Generalized Epilepsy, focal onset seizures and/or childhood epilepsy with centrotemporal spikes.

In one aspect, the present invention relates to a method for treating and/or preventing absence seizures, the method comprising administering 2-(3-(3-(2,4-
10 dimethoxypyrimidin-5-yl)phenyl)-3H-imidazo[4,5-b]pyridin-6-yl)propan-2-ol, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

In one aspect, the present invention relates to a method of modulating or diminishing spike-and-wave discharges in a subject, the method comprising administration of
15 Compound 1, or a pharmaceutically acceptable salt thereof, to the 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
20 treatment and/or prevention of absence seizures in a subject.

In one aspect, the present invention relates to a method of decreasing the time in absence seizure, the number of absence seizures, and/or absence seizure duration in a subject, the method comprising administration of Compound 1, or a pharmaceutically
25 acceptable salt thereof, to the subject in need thereof.

In one aspect, the present invention relates to a method for treating childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE) in a human subject, comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to the
30 subject in need thereof to a subject in need thereof.

In one aspect, the present invention relates to a method for treating absence epilepsy or absence seizures in a human subject in need thereof, comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need
35 thereof.

In one aspect, the present invention relates to a method for treating an epilepsy syndrome or a seizure disorder associated with decreased sleep spindle activity in a human subject in need thereof, comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof

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Compound 1 is a PAM at $\alpha 3$ -containing GABA_ARs, has minimal affinity for the $\alpha 2$ and $\alpha 5$ subunits and no effect on $\alpha 1$ -containing GABA_ARs.

Description of drawings

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Figure 1. EEG recordings obtained in GAERS rats injected systemically with vehicle or Compound 1.

Effect of administration of the indicated doses of compound 1, on absence seizures in GAERS rats. **A:** Vehicle. **B:** 1 mg/kg. **C:** 3 mg/kg. **D:** 10 mg/kg.

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Typical Enlarged sections are indicated below each trace. Voltage and time calibrations in the top left recording apply to all traces.

Conclusion: Administration of compound 1 reduce spike-wave discharges in GAERS rats (a rodent model of spontaneous, genetically determined absence seizures).

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Figure 2. Total time spent in absence seizures by GAERS rats after systemic administration of Compound 1.

A. Total time spent in absence seizures by GAERS rats after systemic administration (at time 0) of the indicated doses of Compound 1. Each data-point represents the total time in seizures observed during the indicated 20 min time period. **B.** Total time in seizure normalised to vehicle-injected rats. * $p < 0.05$; **** $p < 0.0001$.

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Conclusion: Compound 1 significantly decreases the time spent in absence seizures The anti-absence effect of Compound 1 is rapid, potent and long-lasting.

Figure 3. Total time spent in absence seizures by GAERS rats after systemic administration of Compound 1 - Statistical significance of the anti-absence effect of Compound 1 at different time-points after injection.

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Same data as in Figure 2A, showing the statistical significance (Turkey post-hoc test, compared to vehicle-treated GAERS rats) of the total time spent in seizure at each time-point following systemic injection of the indicated doses of Compound 1.

A. 1 mg/kg (n=8). B. 3 mg/kg (n=8). C. 10 mg/kg (n=9). *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Figure 4. Area-under-curve analysis of the anti-absence action of Compound 1.

5 Total time in seizures normalised Area under curve. The data shown in Figure 2 analysed by calculating the area-under-curve for each injected does of Compound 1. *p<0.05; **p<0.01; ****p<0.0001.

Figure 5. Number of absence seizures in GAERS rats after systemic administration of
10 Compound 1.

A. Number of absence seizures in GAERS rats after systemic administration (at time 0) of the indicated doses of Compound 1. Each data-point represents the number of seizures observed during the indicated 20 min time period. B. Same data as in A but normalized to those of vehicle-treated rats. *p<0.05; **p<0.01; ****p<0.0001.

15 Conclusion: Compound 1 significantly decreases the number of absence seizures.

Figure 6. Seizures duration in GAERS rats after systemic administration of Compound 1.

20 A. Average duration of absence seizures in GAERS rats after systemic administration (at time 0) of the indicated doses of Compound 1. Each data-point represents the average duration of absence seizures observed during the indicated 20 min time period. B. Same data as in A, but normalized to those of the vehicle-treated rats. *p<0.05; ***p<0.001; ****p<0.0001.

25 Conclusion: Compound 1 decreases the duration of absence seizures.

Figure 7. Long-lasting anti-absence effect of Compound 1.

30 Total time spent in absence seizures in GAERS rats (normalized to those of vehicle-treated rats) after systemic administration (at time 0) of 10 mg/kg Compound 1. Each data-point represents the total time in seizures observed during the indicated 1 hour time-period. *p<0.05; ***p<0.001.

Conclusion: Compound 1 shows significant long-lasting anti-absence effects.

Figure 8. Compound 1 increases sleep spindles.

35 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 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.

Conclusion: Compound 1 significantly increases sleep spindles..

Detailed description

The present disclosure is based, at least in part, on the finding that administration of Compound 1 provides for modulation of spike-and-wave discharges and absence seizure activity, such as decreased total time in absence seizure, decreased number of absence seizures, and decreased duration of absence seizure.

It is demonstrated that Compound 1 reduces Spike-Wave-Discharges in a rodent model of spontaneous, genetically determined absence seizures (Genetic Absence Epilepsy Rats from Strasbourg, GAERS), thereby suggesting positive effects against generalized absence seizures, and treatment of diseases and disorders with absence seizures (Example 1). These results suggest positive effects against generalized absence seizures, and treatment of diseases and disorders with absence seizures. The compounds of the invention are also useful for the treatment of neurological conditions such as epilepsy including simple partial seizure, complex partial seizure, secondary generalized seizure, further including absence seizure, myoclonic seizure, clonic seizure, tonic seizure, tonic clonic seizure and atonic seizure.

Moreover it is demonstrated, that Compound 1 provides for increase in sleep spindles, such as increased number of sleep spindles and increased duration of sleep spindles (Example 2).

In one aspect, the present invention relates to a method for treating and/or preventing absence seizures, the method comprising administering 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3H-imidazo[4,5-b]pyridin-6-yl)propan-2-ol (Compound 1), or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

Epileptic disorders and absence seizures

Epileptic disorders such as absence epileptic disorders are characterized by having occurrence of spike-and-wave discharges and absence seizure activity. Examples of absence epileptic disorders, including both disorders with typical absences and atypical absences, are:

- ESES/DEE-SWAS
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Lennox-Gastaut (atypical absence seizures)
- Dravet Syndrome (atypical absence seizures)
- Idiopathic Generalized Epilepsy

In some embodiments, the absence seizure is a symptom of an epileptic disease or disorder. In some embodiments, the epileptic disease or disorder is characterized by spike-wave discharges. In some embodiments, the epileptic disease or disorder is electrical status epilepticus during slow-wave sleep (ESES), Developmental/Epileptic Encephalopathy with Spike Wave Activation In Sleep (DEE-SWAS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet Syndrome (atypical absence seizures) or Idiopathic Generalized Epilepsy. In some embodiments, the epileptic disorder includes simple partial seizure, complex partial seizure, secondary generalized seizure, further including absence seizure, myoclonic seizure, clonic seizure, tonic seizure, tonic clonic seizure and/or atonic seizure.

In some embodiments, the absence seizures are typical. In some embodiments, the absence seizures are atypical.

In one aspect, the present invention relates to a method for treating childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE) in a human subject, comprising administering to a subject in need thereof a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

Epileptic disorders and sleep spindles

Some epileptic disorders, such as epilepsy syndromes and seizure disorders, are moreover associated with decreased sleep spindle activity. For example patients with focal epilepsy show a reduction in sleep spindle activity (Schiller et al., 2022, Roliz and Kothare, 2023).

Examples of epilepsy syndromes and seizure disorders associated with decreased sleep spindle activity includes:

- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Lennox-Gastaut syndrome
- Developmental and epileptic encephalopathies (DEE)
- focal onset seizures
- Childhood epilepsy with centrotemporal spikes

In one embodiment, the present invention relates to a method for treating an epilepsy syndrome or a seizure disorder associated with decreased sleep spindle activity in a human subject in need thereof, comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof

In one embodiment, the epilepsy syndrome or seizure disorder is associated with decreased sleep spindle activity. In one embodiment, the epilepsy syndrome or seizure disorder is Childhood absence epilepsy, Juvenile absence epilepsy, Juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, Developmental and epileptic encephalopathies (DEE), focal onset seizures, and/or Childhood epilepsy with centrotemporal spikes.

Sleep spindles are bursts of oscillatory brain activity generated in the reticular nucleus of the thalamus that occur during sleep. Sleep spindles comprise a burst of 12-15 Hz, and occur during stage 2 non-rapid eye movement (NREM) sleep (N2).

Sleep spindle activity 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 Ca^{2+} influx into cortical pyramidal neurons, initiating intracellular cascades involved in generating synaptic plasticity

5 Sleep play a major role in cognitive functions: Sleep spindle density correlates with markers of intelligence, but also with several disorders leading to cognitive deficits and neurological diseases such as epilepsy and epileptic disorders.

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.
10 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 decrease absence seizure activity, such as decreasing total time in absence seizure, decreasing number of absence seizures, and
15 decreasing duration of absence seizure.

Moreover Compound 1 is demonstrated herein to increase number sleep spindles, and moreover increase spindle frequency, spindle power and spindle duration.

20 ***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 present invention relates to a method for treating and/or preventing absence seizures, the method comprising administering Compound 1, or a
25 pharmaceutically acceptable salt thereof, to a subject in need thereof.

In some embodiments, the total time in absence seizure is decreased. In some embodiments, the number of absence seizures is decreased. In some embodiments, the duration of absence seizures is decreased. In some embodiments, the absence
30 seizure activity is decreased within 20 minutes after administration, such as within 10 minutes after administration. In some embodiments, the absence seizure activity is decreased for at least 3 hours after administration, such as 4 hours, such as 5 hours, such as 6 hours, such as 7 hours.

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

5 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 suffering from an epileptic disease or disorder. In some embodiments the

10 epileptic disease or disorder is an absence epileptic disease or disorder.

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 some

embodiments, Compound 1 is administered to the subject as a dose ranging from

15 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 – 100mg/kg. In some embodiments,

Compound 1, or a pharmaceutically acceptable salt thereof, is administered by the oral

route. In one embodiment of the present invention, the treatment by Compound 1 is

20 administered perorally 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 – 100mg/kg.

25 In one embodiment, compound 1 is administered in combination with one or more additional therapeutically active ingredient. In one embodiment the additional therapeutically active ingredient is know for treating epilepsy and epilepsy disorders.

In some embodiments, the subject is less than 21 years of age. In some embodiments,

30 the subject exhibits generalized polyspike or spike and wave discharges at 2 to 6 Hz when measured by electroencephalogram (EEG). In some embodiments, the subject exhibits generalized spike and wave discharges at 3 Hz when measured by electroencephalogram (EEG). In some embodiments, the number of spike-and-wave discharges is decreased.

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In one aspect, the present invention relates to a method of modulating or diminishing spike-and-wave discharges in a subject, the method comprising administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

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In some embodiments, the subject is having, is suspected of having, or at risk of developing an absence seizure. In some embodiments, the subject is a human subject having, suspected of having, or at risk of developing an absence seizure.

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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 absence seizures in a subject.

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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 absence seizures.

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In one aspect, the present invention relates to a method for treating absence epilepsy or absence seizures in a human subject in need thereof, comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

Treatment of absence seizures

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In one aspect, the present invention relates to a method of decreasing the time in absence seizure, the number of absence seizures, and/or absence seizure duration in a subject, the method comprising administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

Pharmaceutically Acceptable Salts

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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,

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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.

Pharmaceutical compositions

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

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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 pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

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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, 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, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (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 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.

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Compound 1 of the invention, together with a conventional adjuvant, carrier, or diluent, 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

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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.

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 compositions exhibiting large therapeutic indexes are preferred.

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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 practitioner.

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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 therapeutic effect. However, it is presently contemplated that pharmaceutical

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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 certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o.

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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.

Definitions

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The term "absence seizure activity" as used herein generally refers to an absence seizure, such as total time in absence seizure, duration of absence seizure and number of absence seizures.

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The term "*preventive treatment*," as used herein to describe the present invention, 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.

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The term "*prophylactic treatment*" as used herein to describe the present invention, 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 and/or preventing absence seizures, the method comprising administering 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.
- 20 2. The method according to item 1, wherein the absence seizure is a symptom of an epileptic disease or disorder.
- 25 3. The method according to any one of the preceding items, wherein the subject is suffering from an epileptic disease or disorder.
4. The method according to any one of items 2 or 3, wherein the epileptic disease or disorder is characterized by spike-wave discharges.
- 30 5. The method according to any one of items 2 to 4, wherein the epileptic disease or disorder is electrical status epilepticus during slow-wave sleep (ESES), Developmental/Epileptic Encephalopathy with Spike Wave Activation In Sleep (DEE-SWAS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet Syndrome (atypical absence seizures) or Idiopathic Generalized Epilepsy.

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- 5 6. The method according to any one of items 2 to 5, wherein the epileptic disorder includes simple partial seizure, complex partial seizure, secondary generalized seizure, further including absence seizure, myoclonic seizure, clonic seizure, tonic seizure, tonic clonic seizure and/or atonic seizure.
7. The method according to any one of the preceding items, wherein the absence seizures are typical.
- 10 8. The method according to any one of the preceding items wherein the absence seizures are atypical.
9. The method according to any one of the preceding items, wherein the absence seizure activity is decreased.
- 15 10. The method according to any one of the preceding items, wherein the total time in absence seizure is decreased.
11. The method according to any one of the preceding items, wherein the number of absence seizures is decreased.
- 20 12. The method according to any one of the preceding items, wherein the duration of absence seizures is decreased.
- 25 13. The method according to any one of the preceding items, wherein the absence seizure activity is decreased within 20 minutes after administration, such as within 10 minutes after administration.
- 30 14. The method according to any one of the preceding items, wherein the absence seizure activity is decreased for at least 3 hours after administration, such as 4 hours, such as 5 hours, such as 6 hours, such as 7 hours.
15. The method according to any one of the preceding items, wherein the subject is less than 21 years of age.

16. The method according to any one of the preceding items, wherein the subject exhibits generalized polyspike or spike and wave discharges at 2 to 6 Hz when measured by electroencephalogram (EEG).
- 5 17. The method of item 16, wherein the subject exhibits generalized spike and wave discharges at 3 Hz when measured by electroencephalogram (EEG).
18. The method according to any one of the preceding items, wherein the number of spike-and-wave discharges is decreased.
- 10 19. The method according to any one of the preceding items, wherein the subject is having, is suspected of having, or at risk of developing an absence seizure.
- 15 20. 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 an absence seizure.
- 20 21. The method according to any one of the preceding items, wherein the subject is administered a dose of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol in the range of 0.001 – 100 mg/kg.
22. The method according to any one of the preceding items, wherein 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 oral route.
- 25 23. The method according to any one of the preceding items, wherein the treatment is curative, preventive, protective, palliative, prophylactic, symptomatic, and/or ameliorative.
- 30 24. A method of modulating or diminishing spike-and-wave discharges 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, to the subject in need thereof.

25. 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 absence seizures in a subject.
- 5
26. 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 absence seizures.
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27. A method of decreasing the time in absence seizure, the number of absence seizures, and/or absence seizure duration 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, to the subject in need thereof.
- 15
28. A method for treating childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE) in a human subject, comprising administering to a subject in need thereof a therapeutically effective amount 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 the subject in need thereof.
- 20
29. A method for treating absence epilepsy or absence seizures in a human subject in need thereof, comprising administering 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 the subject in need thereof.
- 25
30. A method for treating an epilepsy syndrome or a seizure disorder associated with decreased sleep spindle activity in a human subject in need thereof, comprising administering 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 the subject in need thereof.
- 30
31. The method according to item 30, wherein the epilepsy syndrome or seizure disorder associated with decreased sleep spindle activity is: Childhood absence epilepsy, Juvenile absence epilepsy, Juvenile myoclonic epilepsy, Lennox-
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Gastaut syndrome, Developmental and epileptic encephalopathies (DEE), focal onset seizures, and/or Childhood epilepsy with centrotemporal spikes.

Examples

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Example 1 - Treatment of absence seizures with compound 1

In this example, the effect of Compound 1 on spontaneous absence seizures in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) (a polygenic model of absence
10 seizures with strong face-, construct- and content-validity (Crunelli et al., 2002)) was studied.

Materials and methods

Animals:

15 Male GAERS rats bred at Cardiff University and 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
20 expert group guidelines (Lidster et al., 2015). All efforts were made to minimize animal suffering and the number of animals used.

Recording and analysis of absence seizures

Adult (250-300 g) male GAERS rats were anaesthetized with isoflurane (2-5%),
25 positioned in a stereotaxic frame and their body temperature maintained at 37°C with a heating pad. They were bilaterally implanted with gold-plated epidural screws (Svenska Dentorama AB, Sweden) in frontal (AP: + 2.0mm, ML: ± 2.0mm), parietal (AP: – 2.2mm, ML: ± 5.5mm) and cerebellar cortices to record the EEG, as previously described by Kronland-Martinet et al, 1987. Animals were allowed to recover from the surgery for at
30 least five days before any experiment commenced.

For a few days before experiments, GAERS rats were connected to the recording apparatus and placed individually in a Plexiglas box within a Faraday cage for 1-2 hours habituation. On the day of recordings, the animals were placed (at 9:00 AM) into the
35 Plexiglas box for 30 minutes (habituation period) followed by 1 hour recording (control

period) before being injected intraperitoneally (ip) with either the vehicle (5% DMSO + 0.03% HpbCD (0.03% hydroxypropyl-beta-cyclodextrine) solution or with different doses of Compound 1. They were then recorded for 3 hours while being continuously monitored by a researcher. Treatment was assigned in a pseudo-random manner with a cross-over design: each animal received a maximum of four different treatments with at least five days between each treatment. In some experiments, GAERS rats were recorded for up to 7 hours after Compound 1 injection.

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 Mk3 1401 (Cambridge Electronic Design, UK). Spike-and-waves discharges (SWDs) were initially detected semi-automatically in the EEG recordings using the SeizureDetect script (kindly provided by Steve Clifford, CED) in Spike2 v7.03 (Cambridge Electronic Design, UK), and then checked by visual inspection. Data were digitally processed and an interictal EEG period of wakefulness was manually selected and used to set a threshold of ± 5 SD of the baseline EEG. To identify SWDs, all crossings above or below the threshold were then grouped into bursts according to five pre-set parameters: a maximum onset interval (0.2s), a maximum interval (0.75 s), a minimum number of spikes (5), a minimum interval within bursts (1 s) and a minimum duration (0.6 s). Identified bursts lasting less than 1 second were discarded. The putative bursts were ultimately classified into SWDs according to the frequency, which was manually set between 5 and 12 Hz to exclude epochs of deep non-REM sleep and artefacts. This semi-automatic detection was further refined by visual inspection. The following parameters were extracted from the EEG data in 20 min epochs: the total time spent in seizure, the total number of seizures and the average duration of a seizure. Data were plotted as raw data or normalized to the results of the vehicle-injected rats.

Statistical evaluation:

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 each dose was assessed by repeated-measurements (RM) two-way-Analysis of Variance (ANOVA) using Sidak correction for multiple comparisons. The main effect of treatment vs vehicle was also measured as the area-under-the-curve (AUC) and analysed with one-way-ANOVA using Dunnett's multiple comparisons test. All

quantitative data in the text and figures are reported as mean $\pm$ SEM, unless stated otherwise.

Results:

5 *Absence seizures*

As shown in Figure 1 and Figure 2 the systemic injection of Compound 1 dose-dependently blocked spontaneous absence seizures of GAERS rats. Whereas 1 mg/kg Compound 1 had no significant effect, 3 mg/kg decreased the total amount spent in seizures by ~50% and a maximal effect of ~95% was observed with 10 mg/kg (Figure 2A). This anti-absence effect was rapid, being already present in the first 20 min post-injection at all doses and was still present at the end of the recording session (3 hours after injection) (Figures 2A and 3). The strength of these results is supported by the statistically significance observed in the raw data (Figures 2A and 3A-C), the results normalized to the vehicle-injected animals (Figure 2B) and the area-under-the-curve analysis (Figure 4). The anti-absence effect of Compound 1 at 10 mg/kg was due to a decrease in both the number of seizures (Figure 5) and the average duration of a seizure (Figure 6).

In a different set of GAERS rats, it was investigated whether the anti-absence effect of Compound 1 lasted more than 3 hours (Figure 7). A single injection of 10 mg/kg Compound 1 was still effective up to 7 hours after injection, a difference that was statistically significant only 1, 2 and 3 hours after injection.

Conclusions

25 *Anti-absence effect of Compound 1*

The results presented demonstrate that Compound 1 rapidly, potently and dose-dependently reduces spontaneous, genetically determined absence seizures in a well-established model of these non-convulsive seizures, i.e. the GAERS rats. This finding conclusively demonstrates that increasing the activity of $\alpha 3$ subunit-containing GABA_ARs does have an anti-absence effect.

The lack of statistical significance in the anti-absence effect of Compound 1 at 4 -7 hours after injection is likely related to the low number of observations (n=2).

Example 2 - Sleep spindle-enhancing activity of compound 1

In this Example the sleep spindles occurring during natural sleep in normal non-epileptic Wistar rats were studied.

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Materials and methods:

Animals:

Male Wistar rats as described in Example 1 were used.

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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 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.

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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 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 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.

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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 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-Martinet 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

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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.

5 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 Students 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.

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Results:

Sleep spindles

As shown in Figure 8, 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 8A). A statistically significant increase in spindle frequency (Figure 1B) and power (Figure 8C) was present at 60 and 140 min after injection, respectively. Moreover, an increase in the average spindle duration (Figure 8D) was observed at 80 and 140 min post-injection.

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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 spindles at late times (>100 min) after injection. Notably, 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.

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Claims

1. A compound for use in the treatment or prevention of absence seizures in a subject, 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.
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2. The compound for use according to claim 1, wherein the absence seizure is a symptom of an epileptic disease or disorder.
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3. The compound for use according to any one of the preceding claims, wherein the subject is suffering from an epileptic disease or disorder.
4. The compound for use according to any one of claims 2 or 3, wherein the epileptic disease or disorder is characterized by spike-wave discharges.
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5. The compound for use according to any one of claims 2 to 4, wherein the epileptic disease or disorder is electrical status epilepticus during slow-wave sleep (ESES), Developmental/Epileptic Encephalopathy with Spike Wave Activation In Sleep (DEE-SWAS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet Syndrome or Idiopathic Generalized Epilepsy.
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6. The compound for use according to any one of the preceding claims, wherein the absence seizure activity is decreased.
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7. The compound for use according to any one of the preceding claims, wherein the absence seizure activity is decreased within 20 minutes after administration, such as within 10 minutes after administration.
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8. The compound for use according to any one of the preceding claims, wherein the absence seizure activity is decreased for at least 3 hours after administration, such as 4 hours, such as 5 hours, such as 6 hours, such as 7 hours.
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9. The compound for use according to any one of the preceding claims, wherein the number of spike-and-wave discharges is decreased.
- 5 10. The compound for use according to any one of the preceding claims, wherein the subject is a human subject having, suspected of having, or at risk of developing an absence seizure.
- 10 11. The compound for use according to any one of the preceding claims, wherein the subject is administered a dose of 2-(3-(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)propan-2-ol in the range of 0.001 – 100 mg/kg.
- 15 12. The compound for use according to any one of the preceding claims, wherein 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 oral route.
- 20 13. 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.
- 25 14. A method for treating and/or preventing absence seizures, 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, to a subject in need thereof.
- 30 15. A method for decreasing time in absence seizure, number of absence seizures, and/or absence seizure duration, the method comprising administering 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.
- 35 16. A method of modulating or diminishing spike-and-wave discharges 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, to the subject in need thereof.

17. 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 and/or prevention of absence seizures.
18. A compound for use in the treatment or prevention of an epilepsy syndromes or seizure disorder associated with decreased sleep spindle activity, 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.
19. The compound for use according to claim 18, wherein the epilepsy syndrome or seizure disorder associated with decreased sleep spindle activity is selected from: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, developmental and epileptic encephalopathies (DEE), focal onset seizures and/or childhood epilepsy with centrotemporal spikes.