

METHODS OF TREATING EPILEPSY AND RELATED DISORDERS
WITH POTENT AND SELECTIVE POTASSIUM CHANNEL ACTIVATORS

FIELD OF THE INVENTION

5 The present invention relates to methods of treating medical conditions with an anti-seizure medication without adverse events. Specifically, the present invention relates to a method of treating epilepsy with a potassium voltage channel activator (Kv7 channel activator) without producing adverse events that are commonly associated with anti-seizure medications.

10 BACKGROUND OF THE INVENTION

Potassium channel activators emerge as promising candidates for treating epilepsy and other neurological disorders. However, ezogabine and other molecules in this class have been dose limited by adverse events (AEs) typical of antiseizure medications (ASMs) including somnolence, nausea, abdominal pain, balance disorder, dizziness, headache, irritability, anxiety, a mood change, memory impairment, sensory disturbance, speech disorder.

There remains a need in new and selective potassium channel activators that could be dosed safely without producing adverse events in patients.

SUMMARY OF THE INVENTION

20 The present invention is directed to treating and preventing medical conditions without
producing adverse events that are associated with antiseizure medications.

In an embodiment, provided is a method of administering a Kv7 channel activator or a pharmaceutically acceptable salt thereof to a person without producing an adverse event that is commonly associated with an antiseizure medication in that person.

25 In another embodiment, provided is a method of treating a medical condition in a patient, including administering to the patient in need of such treatment a therapeutically effective amount of a Kv7 channel activator or a pharmaceutically acceptable salt thereof, wherein the treatment does not result in an adverse event in the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

These and/or other aspects will become apparent and more readily appreciated from the following description of the embodiments, taken in conjunction with the accompanying drawings in which:

5 FIGS. 1A-C are graphs of Power ($(\text{mV}^2/\text{m}^4)/\text{Hz}$) versus Frequency (Hz) showing spectral power in resting-state EEGs. Changes in spectral power of various frequencies at baseline (day -1; blue) and Compound 1 50-mg dose (red). Shading represents confidence intervals.

FIG. 2 is a diagram showing Compound 1 effects on EEG power spectrum. Absolute power increases most prominently at alpha, beta, and gamma frequencies after a Compound 1 50-mg dose and decreases as plasma concentration decreases. Total absolute power during eyes open was calculated as the difference in power in each band for the Compound 1 50-mg dose at predose, T_{max} , and at 6 hours compared to baseline. T_{max} , time to maximal drug concentration.

10

FIG. 3 is a graph of frequency band versus spectral power change from baseline showing dose-dependent effects of Compound 1 on EEG spectral band power. Change from baseline (day -1) in spectral power by frequency band at the time of maximal response following a single dose of Compound 1 (10, 25, and 50 mg). Boxplot depicts the minimum, 25th percentile, median, 75th percentile, and maximum.

15

DETAILED DESCRIPTION OF THE INVENTION

20 The following detailed description is provided to aid those skilled in the art in practicing the present invention. Exemplary embodiments will hereinafter be described in detail. However, these embodiments are only exemplary, and the present disclosure is not limited thereto but rather is defined by the scope of the appended claims. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure.

25

Accordingly, the embodiments are merely described below, by referring to structures and schemes, to explain aspects of the present description. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. The term "or" means "and/or." Expressions such as "at least one of," when preceding a list of elements, modify the entire list of elements and do not modify the individual elements of the list.

30

It will be understood that when an element is referred to as being "on" another element, it can be directly in contact with the other element or intervening elements may be present therebetween. In contrast, when an element is referred to as being "directly on" another element, there are no intervening elements present.

5 It will be understood that, although the terms first, second, third etc. may be used herein to describe various elements, components, regions, layers, and/or sections, these elements, components, regions, layers, and/or sections should not be limited by these terms. These terms are only used to distinguish one element, component, region, layer, or section from another element, component, region, layer, or section. Thus, a first element, component, region, layer, or section discussed below
10 could be termed a second element, component, region, layer, or section without departing from the teachings of the present embodiments.

 It is understood that the terms "comprises" and/or "comprising," or "includes" and/or "including" when used in this specification, specify the presence of stated features, regions, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or
15 more other features, regions, integers, steps, operations, elements, components, and/or groups thereof.

 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description is for describing particular embodiments only and is not intended to
20 be limiting. It will be further understood that the terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the relevant art and the present disclosure, and will not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

 As used in this application, except as otherwise expressly provided herein, each of the following
25 terms shall have the meaning set forth below. Additional definitions are set forth throughout the application. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

 The articles "a" and "an" refer to one or to more than one (*i.e.*, to at least one) of the
30 grammatical object of the article unless the context clearly indicates otherwise. By way of example, "an element" means one element or more than one element.

As used herein, when specific definition is not otherwise provided, the term "substituted" refers to a group substituted with deuterium, a halogen (-F, -Cl, -Br, -I), a hydroxy group (-OH), an amino group (-NH₂), a carboxyl group (-CO₂H), a substituted or unsubstituted C1-C10 amine group, a nitro group (-NO₂), a C1-C10 alkyl group, a C3-C10 cycloalkyl group, a C6-C12 aryl group, a C1-C10 alkoxy group, a C1 to C10 trifluoroalkyl group such as a trifluoromethyl group (-CF₃) and the like, or a cyano group (-CN) instead of at least one hydrogen of a substituting group or compound.

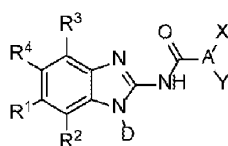
Additional aspects will be set forth in part in the description which follows and, in part, will be apparent from the description.

The starting materials useful for making the pharmaceutical compositions of the present invention are readily commercially available or can be prepared by those skilled in the art.

In an embodiment, provided is a method of administering a Kv7 channel activator or a pharmaceutically acceptable salt thereof to a person without producing an adverse event that is commonly associated with an antiseizure medication in that person.

In another embodiment, provided is a method of treating a medical condition in a patient, including administering to the patient in need of such treatment a therapeutically effective amount of a Kv7 channel activator or a pharmaceutically acceptable salt thereof, wherein the treatment does not result in an adverse event in the patient. The adverse event may include somnolence, nausea, abdominal pain, balance disorder, dizziness, headache, irritability, anxiety, a mood change, memory impairment, sensory disturbance, speech disorder, or a combination thereof, but is not limited thereto.

The Kv7 channel activator may have the following chemical formula:



wherein

D is optionally substituted C₂₋₅ alkyl or optionally substituted phenyl, wherein the optional substituents are selected from -CH₃ and F;

A is C₁₋₆ alkyl;

X is H, F, -CH₃, -CF₃, -SCF₃, pyridinyl, optionally substituted C₁₋₃ alkyl, optionally substituted phenyl, or optionally substituted cyclobutyl, wherein the optional substituent is F;

Y is H, F, -OH, or -CH₃;

R¹ is H, C₃₋₄ hydroxyalkyl, -CN, -OH, -CF₃, -OCHF₂, optionally substituted C₃₋₅ heterocyclyl, optionally substituted C₁₋₅ alkyl, optionally substituted C₁₋₇ alkoxy, -NR^AR^B, or halogen, wherein the optional substituents are selected from -OH and F;

R² is H, halogen, -CN, -OCH₃, -COR^A, -CF₃, -OCF₃, optionally substituted C₁₋₂ alkyl, wherein the optional substituents of R² are selected from -OCH₃ and -COR^A;

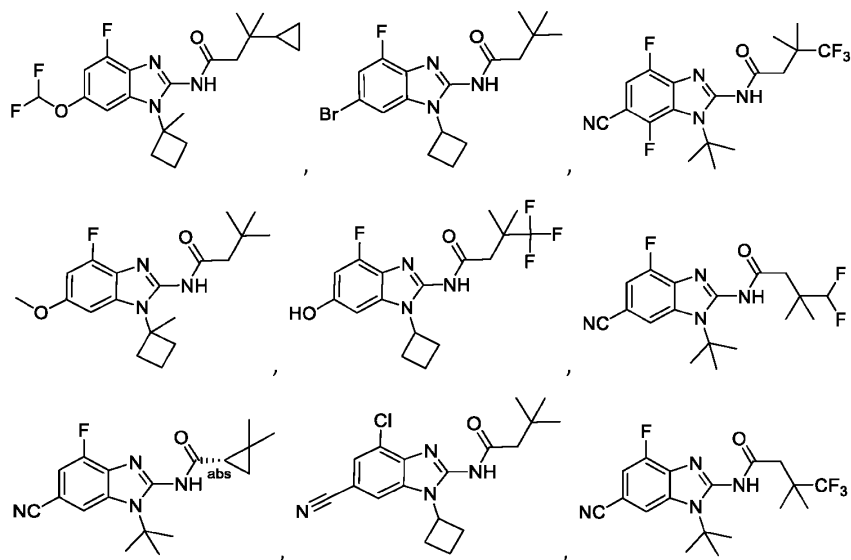
R³ is H, halogen, -CF₃, -OCHF₂, -OCF₃, or -OCH₃;

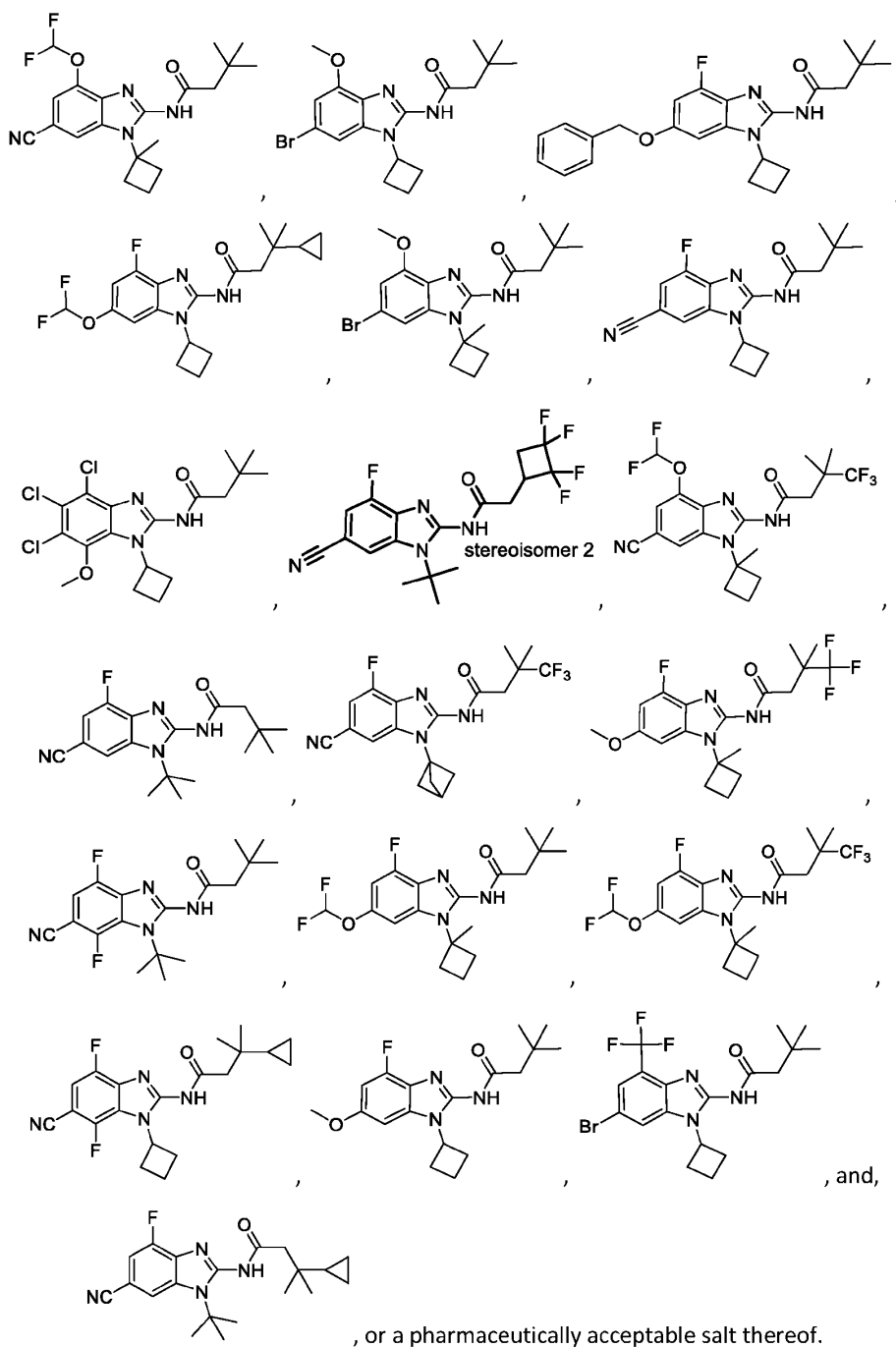
R⁴ is H, halogen, or C₃ hydroxyalkyl; and

R^A and R^B are CH₃;

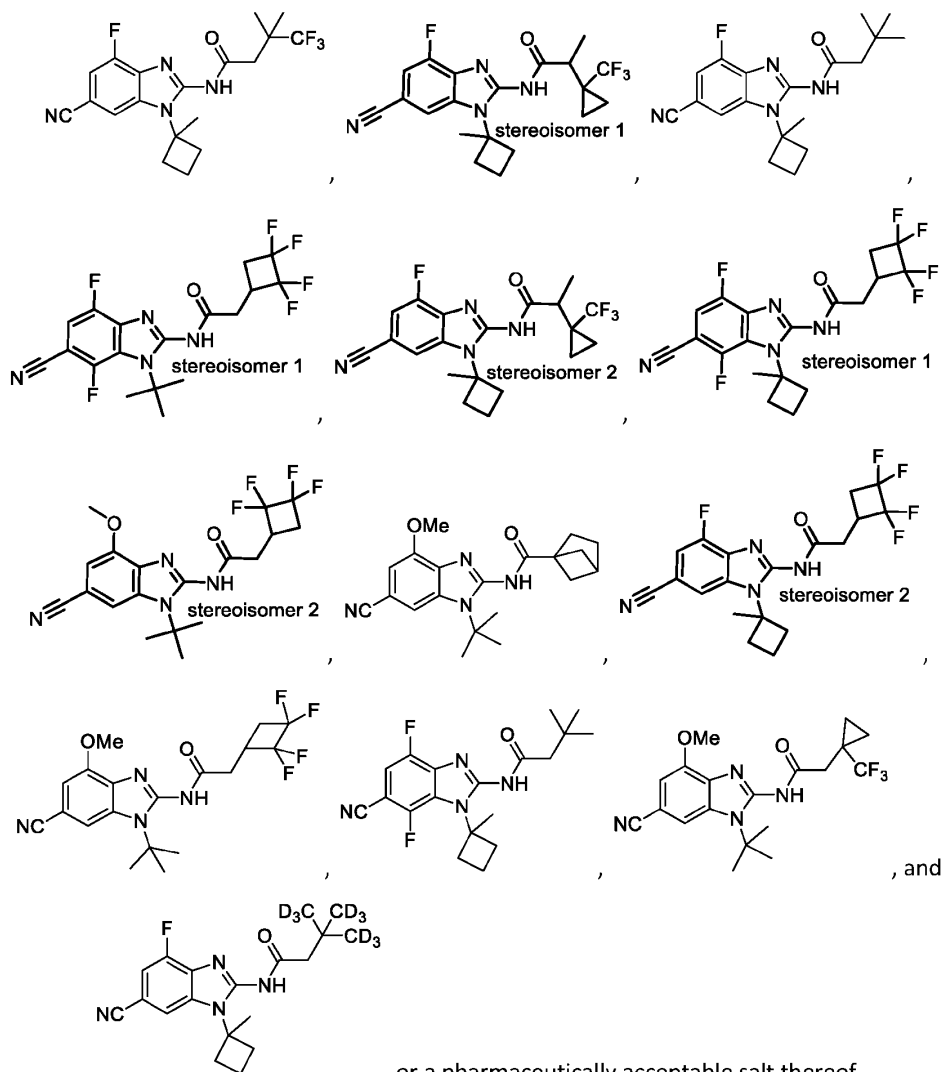
or a pharmaceutically acceptable salt thereof.

For example, the Kv7 channel activator may have the following chemical formula:

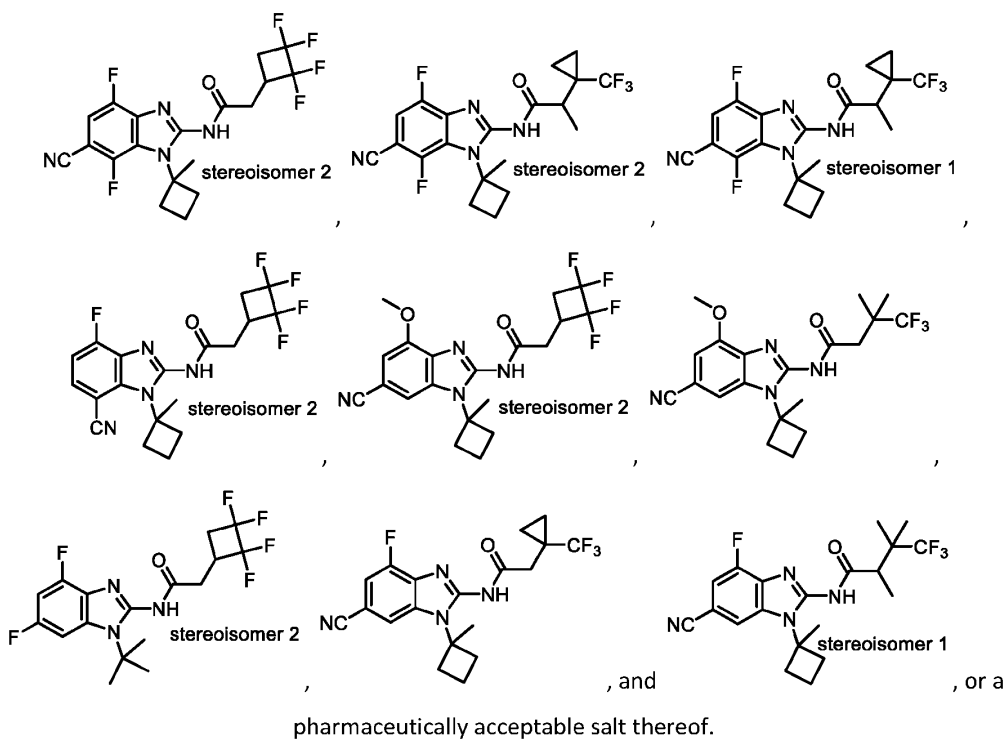




For example, the Kv7 channel activator may have the following chemical formula:

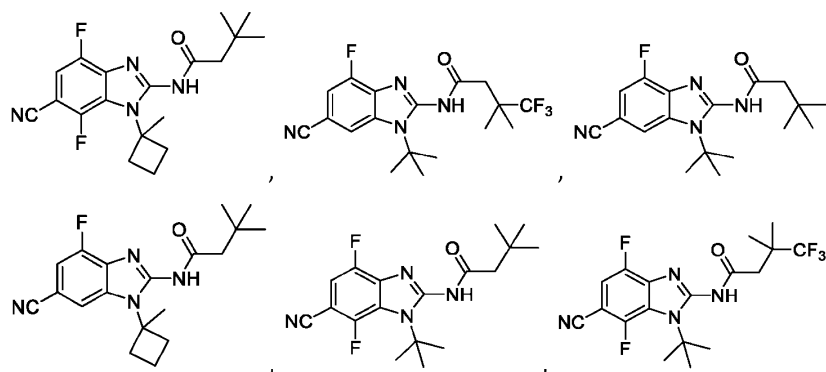


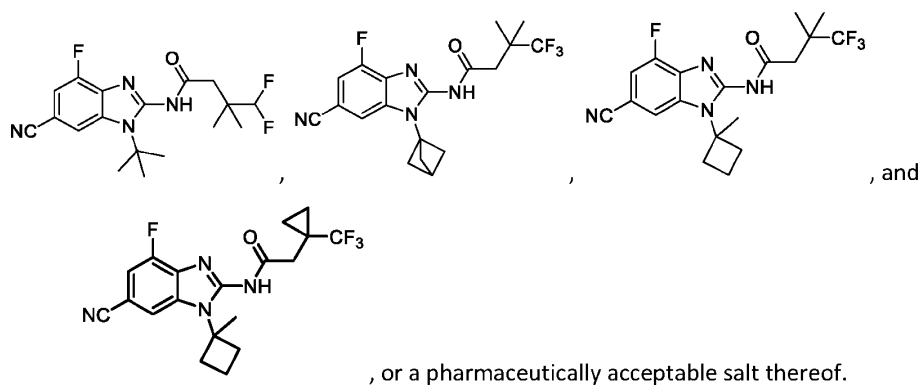
For example, the Kv7 channel activator may have the following chemical formula:



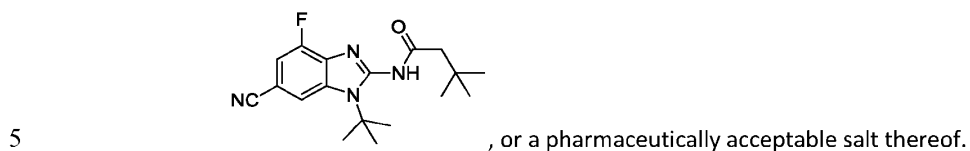
5

For example, the Kv7 channel activator may have the following chemical formula:

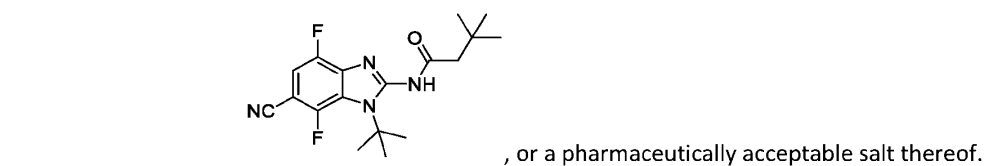




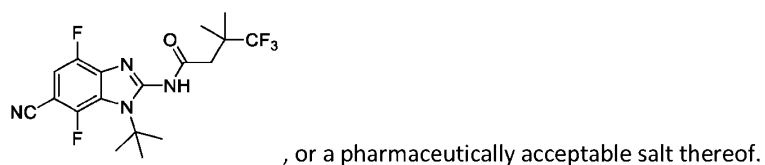
For example, the Kv7 channel activator may have the following chemical formula:



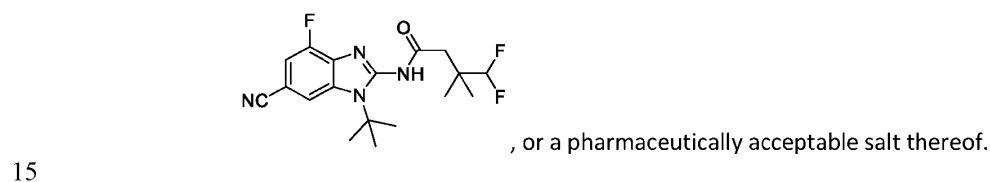
For example, the Kv7 channel activator may have the following chemical formula:



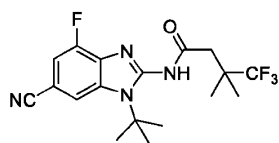
For example, the Kv7 channel activator may have the following chemical formula:



For example, the Kv7 channel activator may have the following chemical formula:

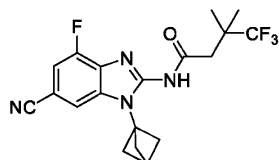


For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

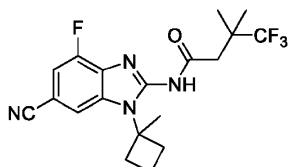
For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

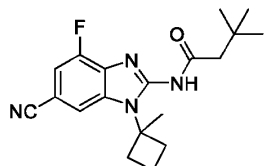
5

For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

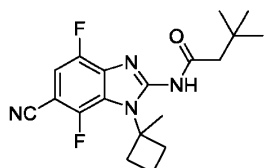
For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

10

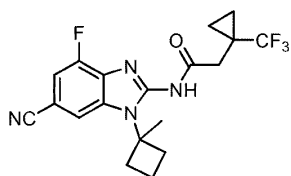
For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

15

For example, the Kv7 channel activator may have the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

The medical condition may be an epilepsy-related disorder, for example, focal epilepsy, pain, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, tinnitus, epileptic encephalopathy, treatment-resistant epilepsy, congenital neurological disorder with intellectual disability or epileptic encephalopathy, severe epileptic encephalopathies, congenital neurodevelopmental disorder with phenotypes of non-syndromic intellectual disability or epileptic encephalopathy, epileptic spasms, epileptic encephalopathy, early infantile epileptic encephalopathy 7, early infantile epileptic encephalopathy with delayed psychomotor development, or a combination thereof.

The medical condition may be a depressive disorder, for example, major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

The medical condition may be a neurological or neurodegenerative disorder, for example, amyotrophic lateral sclerosis, bipolar disorder, treatment resistant and major depression, general anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, dementia, agitation, apathy, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, Rett syndrome, eating disorders, conduct disorder, neurodegenerative disorders, pain disorders, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer's disease, drug addiction, tinnitus, mental retardation, obsessive-compulsive disorder, spinal muscular atrophy, radiation therapy, multiple sclerosis, chronic cerebellar ataxia, cervical spondylotic myelopathy, spinal cord injury, hereditary cerebellar ataxia, Tourette syndrome, autism spectrum disorder, schizophrenia, fragile X syndrome, Parkinson's Disease, Huntington's disease, or any combination thereof.

The medical condition may be a pain disorder, for example, acute pain, chronic pain, neuropathic pain, nociceptive pain, or radicular pain. The pain disorder may be migraine, inflammatory pain, persistent pain, cancer pain, or postoperative pain.

5 The Kv7 channel activator or a pharmaceutically acceptable salt thereof may be administered in an amount of 10 mg, 25 mg, or 50 mg. The Kv7 channel activator or a pharmaceutically acceptable salt thereof may be administered daily. The Kv7 channel activator or a pharmaceutically acceptable salt thereof may be administered on Day 1, Day 5, or Day 9 of the treatment.

10 The pharmacodynamic effects of the Kv7 channel activator may be assessed using electroencephalogram ("EEG") spectral power. In some examples, a change from baseline in spectral power of alpha, beta, or gamma frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by EEG, may be greater than change from baseline in spectral power of delta or theta frequency bands. In other examples, a change from baseline in spectral power of alpha, beta, and gamma frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by EEG, may be greater than change from baseline in spectral power of delta and theta frequency bands. In still other examples, a change from baseline in spectral power of frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by EEG, is substantially as shown in Figure 1 below. The single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof may be 10 mg, 25 mg, or 50 mg.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

25 Novel, Selective Kv7.2/7.3 Potassium Channel Activator, Compound 1, Demonstrates Dose-Dependent Pharmacodynamic Effects on EEG Parameters in Healthy Adults

Objective:

30 Assess the PD effects of single doses of Compound 1 on EEG spectral power in healthy adults.

Rationale:

Compound 1 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels, a clinically validated target in epilepsy. In preclinical studies, Compound 1 showed minimal GABA_A receptor activation and exhibited potent anti-seizure efficacy in the maximal electroshock seizure model without negatively impacting neurobehavior or motor function (ILAE 2023 poster P015, AES 2023 poster 2.249). Ezogabine and other molecules in this class have been dose limited by adverse events (AEs) typical of antiseizure medications (ASMs) including somnolence (Eatock et al. 2007, Barrese et al. 2010, Potiga prescribing information 2012). In a Phase 1 study, Compound 1 was safe and well tolerated at single doses up to 100 mg without dose-limiting AEs (AES poster 3.265). In this study, we assessed the pharmacodynamic effects of single doses of Compound 1 on electroencephalogram (EEG) spectral power in healthy adults.

Quantitative Spectral Analysis:

Quantitative EEG (qEEG) is an advanced technique to quantify and analyze electrical activity of the brain in a standardized and objective manner, helping clinicians and researchers gain insights into brain function.

Spectral analysis is a fundamental method used in qEEG to quantify the power, spatial distribution, and peaks of rhythmic brain activity. Changes in spectral power have been linked to epileptogenesis and seizure prediction and detection in epilepsy and cognitive changes, awareness, and treatment efficacy in neurological disorders.

In this study, the EEGs were preprocessed to remove muscle and eye artifacts and environmental noise. Current source density analysis was applied to estimate the radial current flow at the scalp, leading to more spatially distinct and reference-free topographies.

FFT was applied to extract the spectrum in epochs of 3 seconds. From these, the peak frequency, power at peak, and the corresponding topography in the canonical frequency bands (delta [1-3.5 Hz], theta [3.5-7.5 Hz], alpha [7.5-13 Hz], beta [13-30 Hz], and gamma [30-100 Hz]) were derived

Methods:

This was a phase 1 open label clinical trial conducted in 11 healthy adult males/females aged 18-55 years. All subjects underwent sequential EEG recordings with the international 10-20 electrode setup at Day -1, Day 1, Day 5 and Day 9. Subjects received single doses of 10, 25, and 50 mg of Compound 1

(standard release formulation) on Days 1, 5 and 9 in a randomized sequence. On Day -1, no dose was given to assess the baseline. EEG measurements, collected by Stratus (Irving, Texas, USA), included a 5-minute period of resting state with eyes open and 5 minutes of resting state with eyes closed at baseline, pre-dose, 1h, 2h, 3h, 4h and 6h post-drug intake. Epilog NV (Ghent, Belgium) performed quantitative spectral analysis (using Fast Fourier Transformation) of all EEG recordings to assess pharmacodynamic effects over time. Cluster-based permutation analysis was conducted to identify statistically significant differences. Plasma levels of Compound 1 were quantified at corresponding time points with EEG for assessment of concentration-response relationships.

10 Results:

Eleven healthy adult males and females were enrolled and received Compound 1. Compound 1 increased alpha power in the resting-state EEG of healthy volunteers (FIG. 1). This effect was also seen in the beta and gamma bands. A minimal effect was observed in delta and theta frequencies, which are frequencies associated with somnolence and sleep. PD effects of Compound 1 on EEG power spectrum correlated with Compound 1 plasma concentration (FIG. 2). Absolute power increased across the frequency spectra with drug exposure, then declined as plasma concentration decreased.

Compound 1 was well tolerated at all doses tested. Dose-dependent effects of Compound 1 were observed in EEG spectral power in all frequency bands (FIG. 3). The greatest increases in spectral power were seen in the alpha, beta, and gamma bands. Changes were seen across all EEG channels, indicating a global central nervous system (CNS) drug effect. Furthermore, positive correlations were found between spectral power and Compound 1 plasma concentration at the time of maximal response in all frequency bands.

25 Conclusion:

The pharmacodynamic activity of Compound 1 in the brain of healthy adults was demonstrated in this study by dose- and concentration-dependent increases in EEG spectral power across all canonical frequency bands. Unlike prior reports (Biondi et al. 2022) where the EEG effects of a Kv7.2/7.3 activator showed the greatest power increase in the delta band, the highest spectral power increases with Compound 1 were seen in the alpha, beta and gamma bands. While changes in spectral power were observed across all frequency bands with Compound 1, the reduced impact on slower frequencies (delta and theta) is consistent with the low incidence of CNS AEs such as somnolence seen in the first-in-

human Compound 1 Phase 1 study (AES 2023 poster 3.265). These study results support the continued development of Compound 1 for epilepsy and its potential to deliver anti-seizure efficacy without dose-limiting AEs.

5 Phase 1 Multiple Ascending Dose Studies Demonstrate Favorable Safety and Tolerability of Compound 1,
a Novel Kv7 Potassium Channel Activator

Rationale:

10 Despite a number of approved antiseizure medications (ASMs) for treating epilepsy, many patients are refractory to treatment and suffer from burdensome side effects that limit their utility. CNS adverse events (AEs), such as somnolence and cognitive/mood disturbances, negatively impact quality of life and lead to non-adherence. Thus, an unmet need exists for more effective agents with favorable tolerability profiles. Compound 1 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels in late-stage clinical development for epilepsy and neuropsychiatric disorders. In comparison
15 with ezogabine and its analogues, Compound 1 belongs to a significantly different structural class and was rationally designed to differentiate on key properties. In preclinical studies, Compound 1 demonstrated minimal GABA_A receptor activation and exhibited potent anti-seizure efficacy in the MES model without negative effects on neurobehavior or motor function. A Phase 1 EEG study confirmed CNS target engagement of Compound 1. Initial Phase 1 studies demonstrated favorable safety and
20 tolerability of Compound 1 with no dose-limiting AEs. The objective of this analysis was to assess the safety and tolerability of Compound 1 across multiple ascending dose (MAD) studies completed to date.

Methods:

25 Results were pooled from Phase 1 placebo-controlled MAD studies. Healthy adults aged 18-55 years were included, and participants were randomized to oral Compound 1 immediate release (10, 25, 40, 80, or 120 mg daily), extended-release (25, 50, or 75 mg daily), or matching placebo, and treated for up to 15 days. Safety evaluations throughout the studies included AE monitoring, clinical laboratory tests, vital signs, ECGs, physical examinations, and suicidality assessments.

30 Results:

Across the MAD cohorts, 66 participants received Compound 1 (N=53) or placebo (N=13). Adverse events occurring in ≥5% of participants across the pooled Compound 1 cohorts are presented in

Table 1. There were low rates of CNS-related AEs; no somnolence was reported. The majority of AEs were mild and resolved spontaneously. There were no deaths, serious AEs, severe AEs, or dose-limiting toxicities. No AEs were reported among participants receiving Compound 1 75 mg extended release (n=12), the highest dose currently utilized in Phase 2/3 studies.

Conclusion:

Compound 1 was safe and well tolerated in multiple-dose Phase 1 studies across all doses evaluated for up to 15 days. Adverse events typically associated with other ASMs, such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in the treatment of epilepsy and other neuropsychiatric disorders. These findings support the continued clinical development of Compound 1. Patients are currently being enrolled in multiple Phase 2/3 studies evaluating the efficacy and safety of Compound 1 in focal and generalized epilepsy as well as neuropsychiatric disorders.

Table 1. Compound 1 dosing is not associated with CNS AEs typical of other ASMs in healthy volunteers.

Pooled CNS AEs	BHV-7000 MAD Pooled N=29	XEN1101 MAD Pooled N=18
Somnolence	0%	39%
Headache	21%	39%
Balance disorder/ dizziness	10%	34%
Memory impairment	0%	28%
Sensory disturbance	0%	11%
Speech disorder	0%	33%

XEN1101, also known as Encukalner, is represented by the formula C₂₃H₂₉FN₂O, and its full chemical name is N-[4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide.

Table 2. TEAEs Occurring in $\geq 5\%$ of Participants Receiving Compound 1 in MAD Cohorts.

Adverse Event, n (%)	Placebo (N=13)	Compound 1 (N=53)
Headache	3 (23.1)	6 (11.3)
Back pain	0	6 (11.3)
Constipation	3 (23.1)	3 (5.7)
Dizziness	2 (15.4)	3 (5.7)

Data are pooled across studies evaluating up to 15 days of dosing. Compound 1 cohorts included 10 mg (n=5), 25 mg, (n=6), 40 mg (n=6), 80 mg (n=6), and 120 mg (n=6) with an immediate release formulation; and 25 mg (n=6), 50 mg (n=6), and 75 mg (n=12) with an extended-release formulation

Throughout this application, various publications are referenced by author name and date, or by patent number or patent publication number. The disclosures of these publications are hereby incorporated in their entireties by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. For example, pharmaceutically acceptable salts other than those specifically disclosed in the description and Examples herein can be employed. Furthermore, it is intended that specific items within lists of items, or subset groups of items within larger groups of items, can be combined with other specific items, subset groups of items or larger groups of items whether or not there is a specific disclosure herein identifying such a combination.

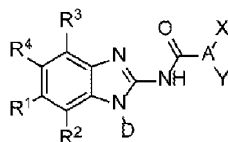
CLAIMS

1. A method of administering a Kv7 channel activator or a pharmaceutically acceptable salt thereof to a person without producing an adverse event that is commonly associated with an antiseizure medication in that person.

2. A method of treating a medical condition in a patient without producing an adverse event that is commonly associated with an antiseizure medication in that patient, the method comprising administering to the patient in need of such treatment a therapeutically effective amount of a Kv7 channel activator or a pharmaceutically acceptable salt thereof.

3. The method according to Claim 1 or 2, wherein the adverse event comprises somnolence, nausea, abdominal pain, balance disorder, dizziness, headache, irritability, anxiety, a mood change, memory impairment, sensory disturbance, speech disorder, or a combination thereof.

4. The method according to any one of Claims 1 to 3, wherein the Kv7 channel activator has the following chemical formula:



wherein

D is optionally substituted C₂₋₅ alkyl or optionally substituted phenyl, wherein the optional substituents are selected from -CH₃ and F;

A is C₁₋₆ alkyl;

X is H, F, -CH₃, -CF₃, -SCF₃, pyridinyl, optionally substituted C₁₋₃ alkyl, optionally substituted phenyl, or optionally substituted cyclobutyl, wherein the optional substituent is F;

Y is H, F, -OH, or -CH₃;

R¹ is H, C₃₋₄ hydroxyalkyl, -CN, -OH, -CF₃, -OCHF₂, optionally substituted C₃₋₅ heterocyclyl, optionally substituted C₁₋₅ alkyl, optionally substituted C₁₋₇ alkoxy, -NR^AR^B, or halogen, wherein the optional substituents are selected from -OH and F;

R² is H, halogen, -CN, -OCH₃, -COR^A, -CF₃, -OCF₃, optionally substituted C₁₋₂ alkyl, wherein the optional substituents of R² are selected from -OCH₃ and -COR^A;

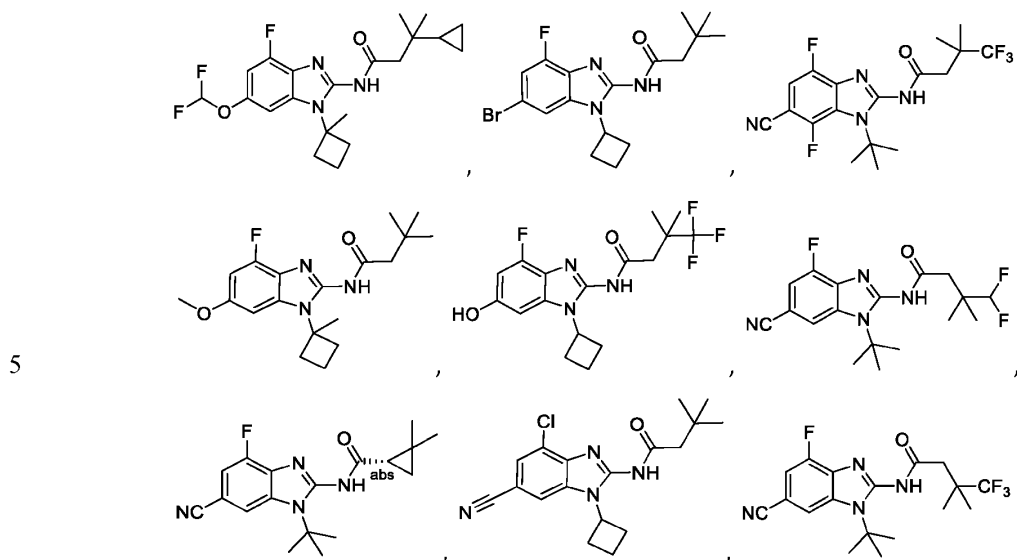
R³ is H, halogen, -CF₃, -OCHF₂, -OCF₃, or -OCH₃;

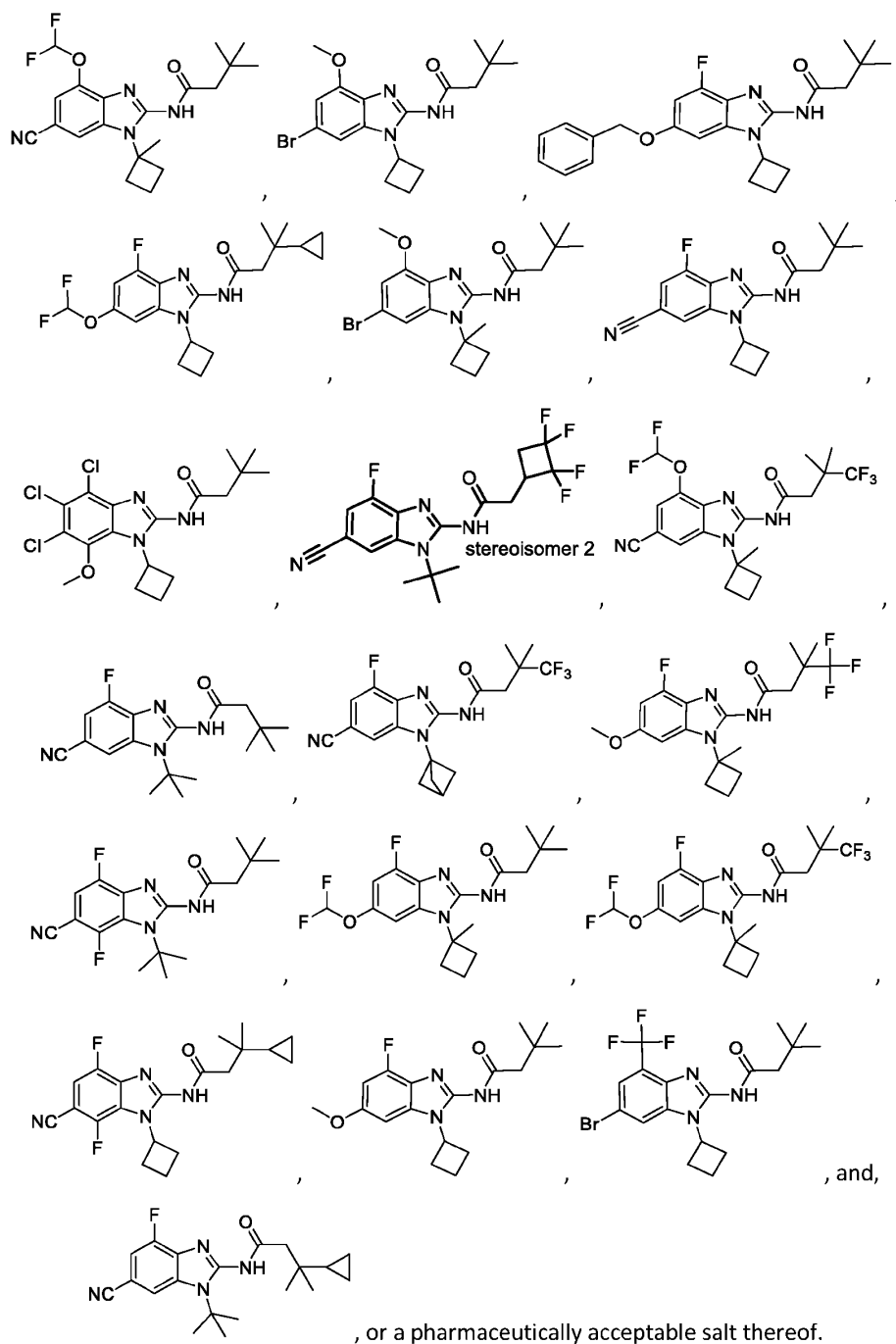
R⁴ is H, halogen, or C₃ hydroxyalkyl; and

R^A and R^B are CH₃;

or a pharmaceutically acceptable salt thereof.

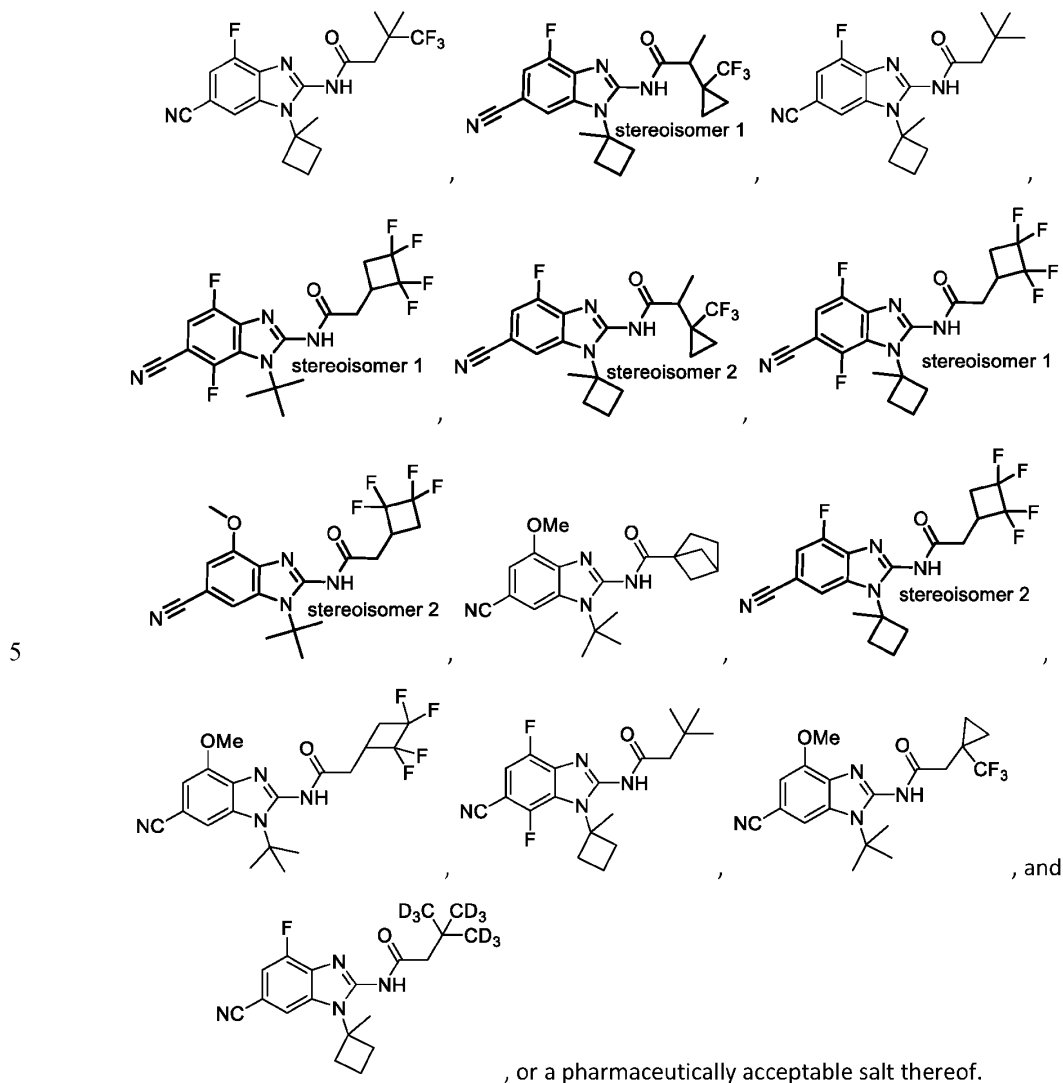
5. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:





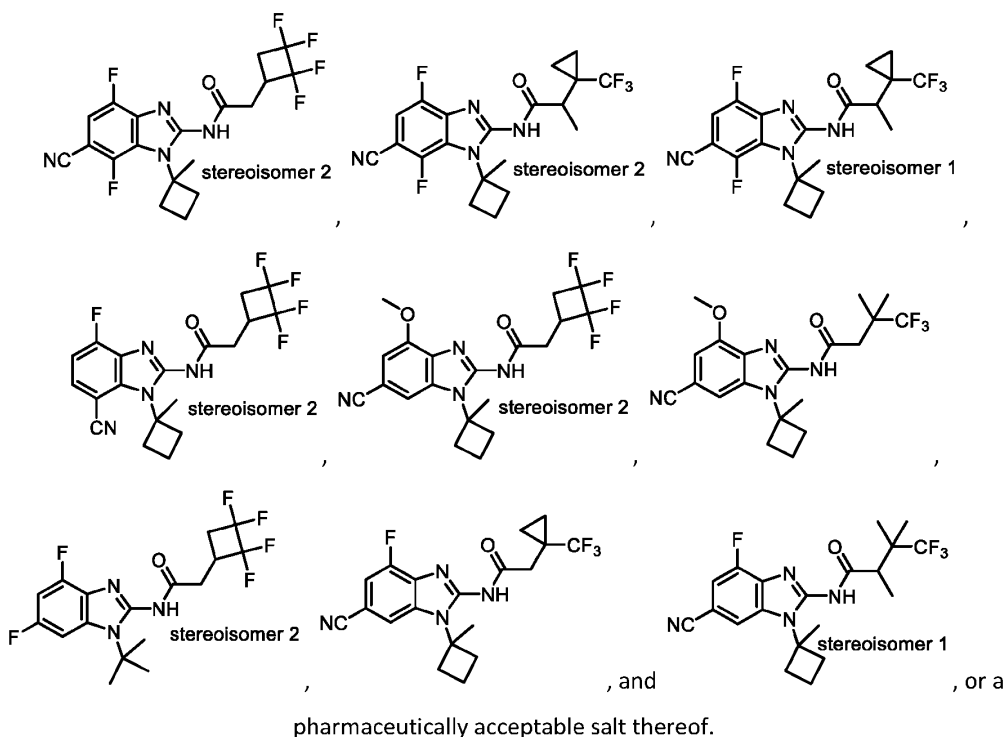
5

6. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



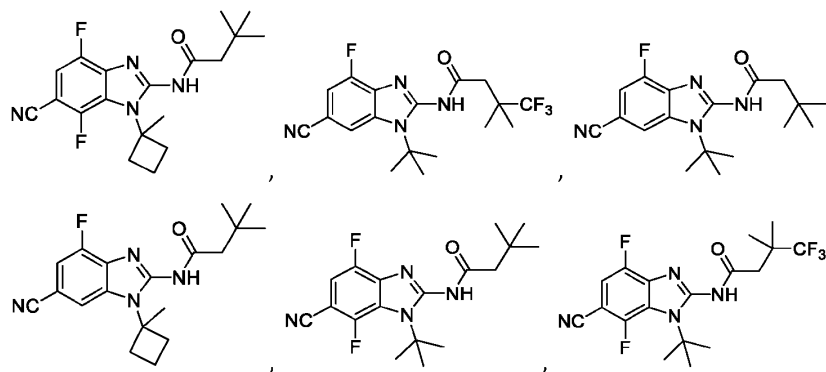
7. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:

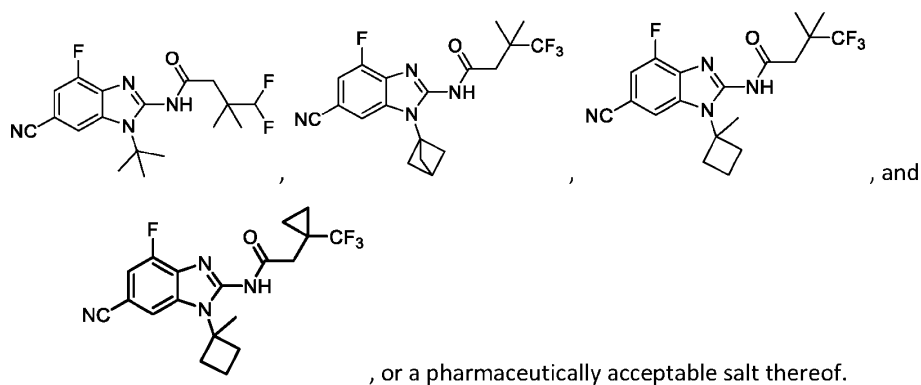
10



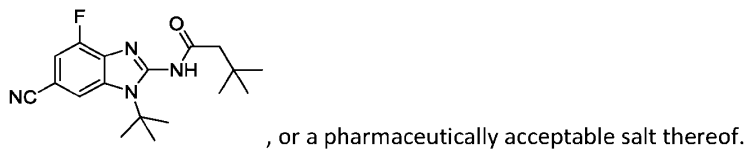
5

8. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:

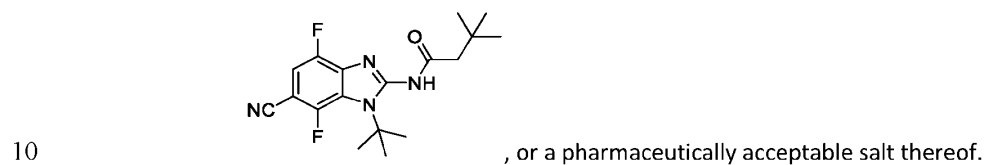




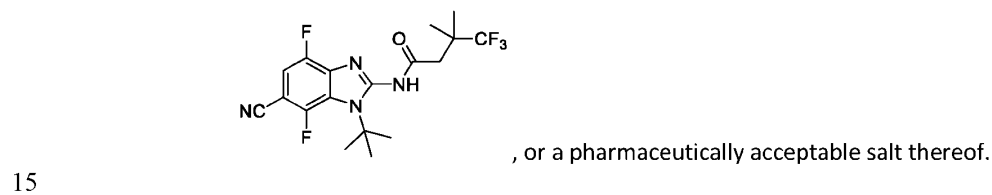
9. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator
- 5 has the following chemical formula:



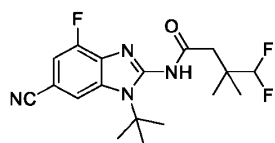
10. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator
- has the following chemical formula:



11. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator
- has the following chemical formula:

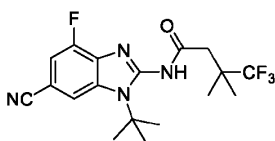


12. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator
- has the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

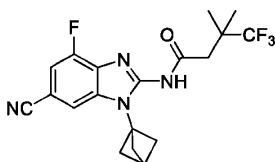
13. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



5

, or a pharmaceutically acceptable salt thereof.

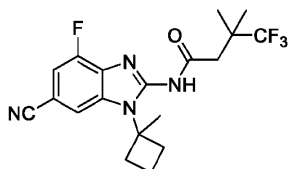
14. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



10

, or a pharmaceutically acceptable salt thereof.

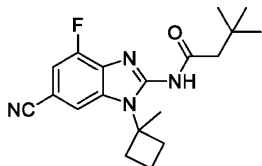
15. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

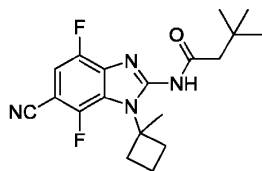
15

16. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



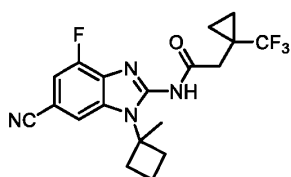
, or a pharmaceutically acceptable salt thereof.

17. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

18. The method according to any one of Claims 1 to 4, wherein the Kv7 channel activator has the following chemical formula:



, or a pharmaceutically acceptable salt thereof.

19. The method according to any one of Claims 1-18, wherein the medical condition is an epilepsy-related disorder.

20. The method according to any of Claim 19, wherein the epilepsy-related disorder is focal epilepsy, pain, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, tinnitus, epileptic encephalopathy, treatment-resistant epilepsy, congenital neurological disorder with intellectual disability or epileptic encephalopathy, severe epileptic encephalopathies, congenital neurodevelopmental disorder with phenotypes of non-syndromic intellectual disability or epileptic encephalopathy, epileptic spasms, epileptic encephalopathy, early infantile epileptic encephalopathy 7, early infantile epileptic encephalopathy with delayed psychomotor development, or a combination thereof.

21. The method according to any one of Claims 1-18, wherein the medical condition is a depressive disorder.

22. The method according to Claim 21, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective

disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

5 23. The method according to any one of Claims 1-18, wherein the medical condition is a neurological or neurodegenerative disorder.

 24. The method according to Claim 23, wherein the neurological or neurodegenerative disorder is amyotrophic lateral sclerosis, bipolar disorder, treatment resistant and major depression,
10 general anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, dementia, agitation, apathy, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, Rett syndrome, eating disorders, conduct disorder, neurodegenerative disorders, pain disorders, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment,
15 mild cognitive impairment due to Alzheimer's disease, drug addiction, tinnitus, mental retardation, obsessive-compulsive disorder, spinal muscular atrophy, radiation therapy, multiple sclerosis, chronic cerebellar ataxia, cervical spondylotic myelopathy, spinal cord injury, hereditary cerebellar ataxia, Tourette syndrome, autism spectrum disorder, schizophrenia, fragile X syndrome, Parkinson's Disease, Huntington's disease, or a combination thereof.

20 25. The method according to any one of Claims 1-18, wherein the medical condition is a pain disorder.

 26. The method according to Claim 25, wherein the pain disorder is acute pain, chronic pain,
25 neuropathic pain, nociceptive pain, or radicular pain.

 27. The method according to Claim 25, wherein the pain disorder is migraine, inflammatory pain, persistent pain, cancer pain, or postoperative pain.

30 28. The method according to any one of Claims 1-27, wherein the Kv7 channel activator or a pharmaceutically acceptable salt thereof is administered in an amount of 10 mg, 25 mg, or 50 mg.

29. The method according to any one of Claims 1-28, wherein the Kv7 channel activator or a pharmaceutically acceptable salt thereof is administered daily.

30. The method according to any one of Claims 1-29, wherein the Kv7 channel activator or a pharmaceutically acceptable salt thereof is administered on Day 1, Day 5, or Day 9 of the treatment.

31. The method according to any one of Claims 1-30, wherein a change from baseline in spectral power of alpha, beta, or gamma frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by electroencephalogram (EEG), is greater than change from baseline in spectral power of delta or theta frequency bands.

32. The method according to any one of Claims 1-31, wherein a change from baseline in spectral power of alpha, beta, and gamma frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by electroencephalogram (EEG), is greater than change from baseline in spectral power of delta and theta frequency bands.

33. The method according to any one of Claims 1-32, wherein a change from baseline in spectral power of frequency bands at the time of maximal response following a single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof, as evidenced by electroencephalogram (EEG), is substantially as shown in Figure 1.

34. The method according to any one of Claims 1-32, wherein the single dose of the Kv7 channel activator or a pharmaceutically acceptable salt thereof is 10 mg, 25 mg, or 50 mg.