KCNT1 INHIBITORS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application Number 62/842,855 filed May 3, 2019, U.S. Provisional Patent Application Number 62/842,858 filed May 3, 2019, U.S. Provisional Patent Application Number 62/842,861 filed May 3, 2019, and U.S. Provisional Patent Application Number 62/982,858 filed February 28, 2020, the contents of each which are incorporated herein by reference in their entirety.

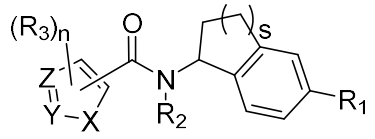
BACKGROUND

[0002] KCNT1 encodes sodium-activated potassium channels known as Slack (Sequence like a calcium-activated K^+ channel). These channels are found in neurons throughout the brain and can mediate a sodium-activated potassium current I_{KNa}. This delayed outward current can regulate neuronal excitability and the rate of adaption in response to maintained stimulation. Abnormal Slack activity have been associated with development of early onset epilepsies and intellectual impairment. Accordingly, pharmaceutical compounds that selectively regulate sodium-activated potassium channels, e.g., abnormal KCNT1, abnormal I_{KNa}, are useful in treating a neurological disease or disorder or a disease or condition related to excessive neuronal excitability and/or KCNT1 gain-of-function mutations.

SUMMARY

[0003] Described herein are compounds and compositions useful for preventing and/or treating a disease, disorder, or condition, e.g., a neurological disease or disorder, a disease, disorder, or condition associated with excessive neuronal excitability and/or a gain-of-function mutation in a gene, for example, KCNT1.

[0004] Thus, in one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula **I-I**:



(**I-I**),

or a pharmaceutically acceptable salt thereof, wherein

X is selected from the group consisting of NH, O, and S, wherein the hydrogen of NH may be substituted with R_3;

Y is selected from N and CH, wherein the hydrogen of CH may be substituted with R_3;

Z is selected from N and CH, wherein the hydrogen of CH may be substituted with R_3, or Z is C when Z is substituted with the $–C(O)N(R_2)-$ moiety;

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

each R_3 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-7}cycloalkyl, 3-7 membered heterocyclyl, $-S(O)_2NR_4R_5$, $-NR_4S(O)R_6$, $-C(O)NR_4R_5$, $-S(O)_2R_6$, and $-O-R_6$, wherein C_{1-6}alkyl is optionally substituted with one or more substituents independently selected from halogen, $-NR_4R_5$, and $-S(O)_2R_6$;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

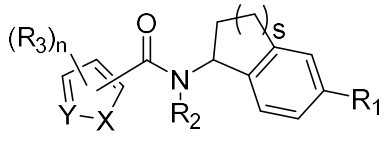
R_4 and R_5 are each independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with oxo; or R_4 and R_5 may be taken together with the nitrogen to which R_4 and R_5 are attached to form a 4-7 membered heterocyclyl optionally substituted with one or more substituents independently selected from halogen, -OH, C_{1-6}alkyl, and C_{1-6}heteroalkyl;

each R_6 is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, phenyl, and benzyl; and

s is 1 or 2;

and a pharmaceutically acceptable excipient.

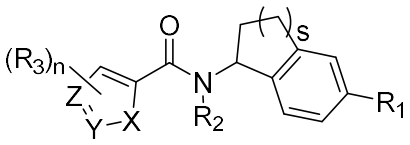
[0005] In some examples, the compound of Formula **I-I** is a compound of Formula **I**:

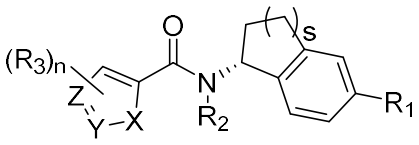


(**I**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I** .

[0006] In some examples, the compound of Formula **I-I** is a compound of Formula **I-Ia** or Formula **I-Ia1**:

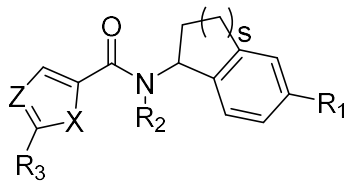


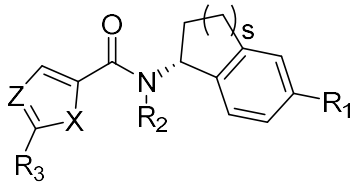
(**I-Ia**),


(**I-Ia1**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[0007] In some examples, the compound of Formula **I-I** is a compound of Formula **I-Ib** or Formula **I-Ib1**:

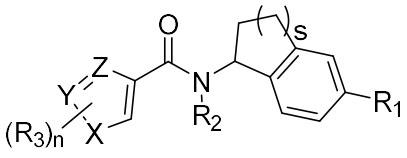


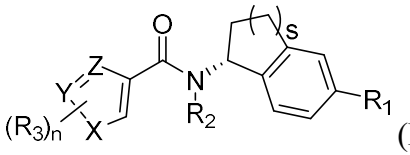
(**I-Ib**), 

(**I-Ib1**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[0008] In some examples, the compound of Formula **I-I** is a compound of Formula **I-Ic** or Formula **I-Ic1**:

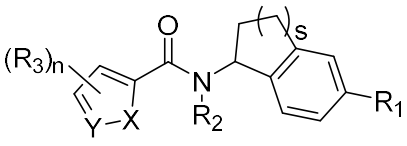


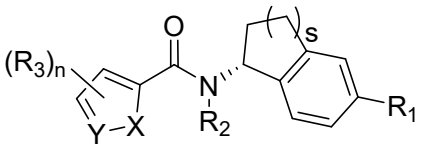
(**I-Ic**), 

(**I-Ic1**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[0009] In some examples, the compound of Formula **I-I** is a compound of Formula **I-a** or Formula **I-a1**:

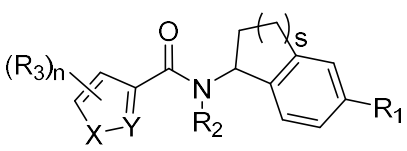


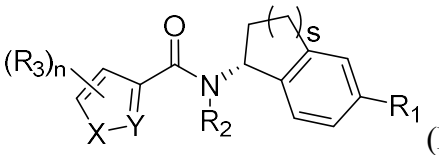
(**I-a**), 

(**I-a1**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[00010] In some examples, the compound of Formula **I-I** is a compound of Formula **I-b** or Formula **I-b1**:

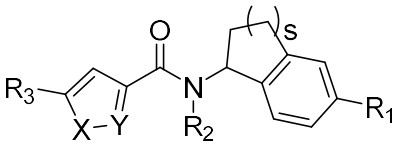
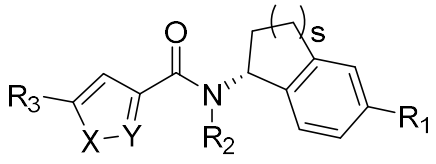


(**I-b**), 

(**I-b1**),

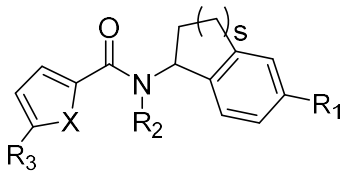
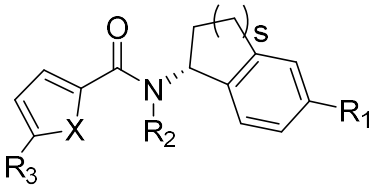
or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[00011] In some examples, the compound of Formula **I-I** is a compound of Formula **I-c** or Formula **I-c1**:


(**I-c**),

(**I-c1**),

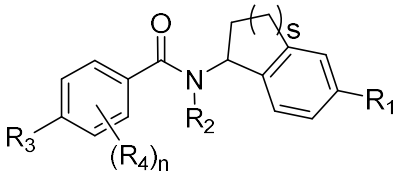
or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[00012] In some examples, the compound of Formula **I-I** is a compound of Formula **I-d** or Formula **I-d1**:


(**I-d**),

(**I-d1**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for Formula **I-I**.

[00013] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula **II**:


(**II**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

R_3 is independently selected from the group consisting of halogen, C_{1-6}alkoxy, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, $-C(O)NR_5R_6$, $-NR_7S(O)_2C_{1-6}$alkyl, $-NR_7S(O)_2C_{3-7}$ cycloalkyl, $-NR_7S(O)_2NR_5R_6$, $-NR_9R_{10}$, $-S(O)_2$-C_{3-6}cycloalkyl, $-S(O)_2-NR_5R_6$, $-S(O)_2$-C_{1-6}alkoxy, and $-S(O)_2$-C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halogen or C_{1-6}alkoxy;

each R_4 is independently selected from the group consisting of C_{1-6}alkyl, halogen, and -OH; wherein R_4 is substituted at the carbon adjacent to R_3 when R_4 is -OH;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

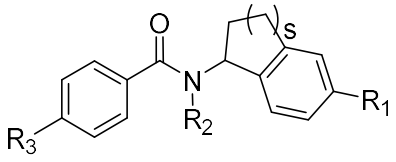
R_5, R_6, R_9, and R_{10} are each independently hydrogen or C_{1-6}alkyl;

each R_7 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and 3-7 membered heterocyclyl, wherein the C_{1-6}alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OH, $-NR_5R_6$, and $-C(O)NR_5R_6$; and

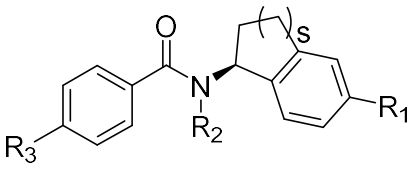
s is 1 or 2;

and a pharmaceutically acceptable excipient.

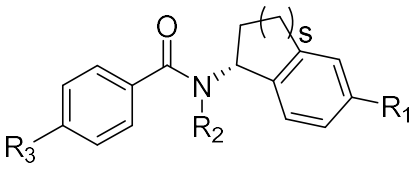
[00014] In some examples, the compound of Formula **II** is a compound of Formula **II-a**, Formula **II-a1**, or Formula **II-a2**:



(**II-a**),



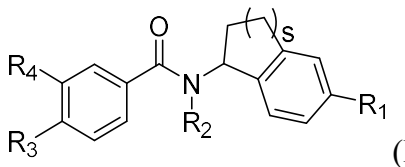
(**II-a1**),



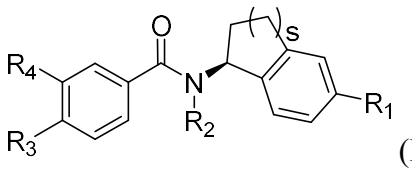
(**II-a2**),

or a pharmaceutically acceptable salt thereof.

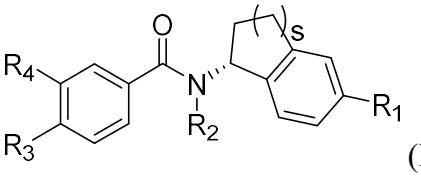
[00015] In some examples, the compound is a compound of Formula **II-b**, Formula **II-b1**, or Formula **II-b2**:



(**II-b**),



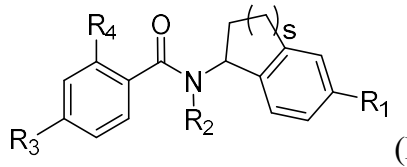
(**II-b1**),



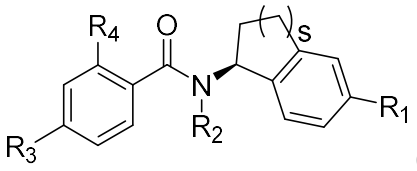
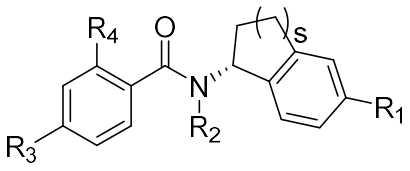
(**II-b2**),

or a pharmaceutically acceptable salt thereof.

[00016] In some examples, the compound of Formula **II** is a compound of Formula **II-c**, Formula **II-c1**, or Formula **II-c2**:

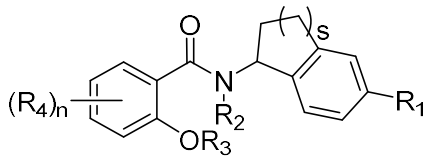


(**II-c**),


(**II-c1**),

(**II-c2**),

or a pharmaceutically acceptable salt thereof.

[00017] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula **III**:


(**III**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

R_3 is hydrogen;

R_4 is each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-NR_7S(O)_2C_{1-6}$alkyl, and $-NR_8C(O)-C_{1-6}$alkyl;

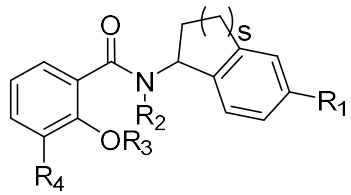
n is selected from the group consisting of 0, 1, 2, 3, and 4;

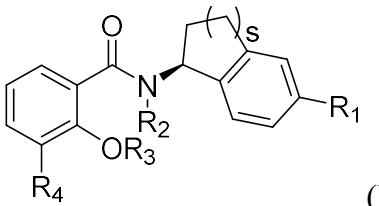
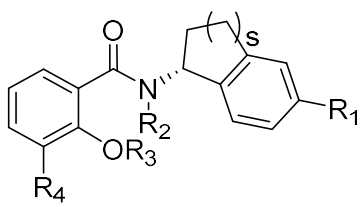
R_7 and R_8 are each independently hydrogen or C_{1-6}alkyl; and

s is 1 or 2;

and a pharmaceutically acceptable excipient.

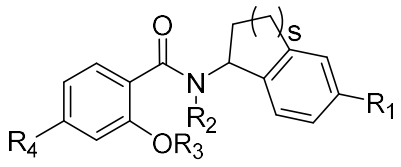
[00018] In some examples, the compound of Formula **III** is a compound of Formula **III-a**, Formula **III-a1**, or Formula **III-a2**:

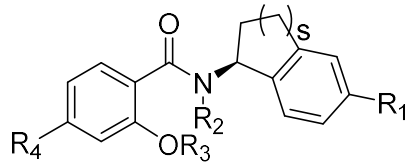

(**III-a**),

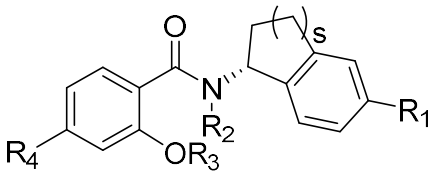

(**III-a1**),

(**III-a2**),

or a pharmaceutically acceptable salt thereof.

[00019] In some examples, the compound of Formula **III** is a compound of Formula **III-b**, Formula **III-b1**, or Formula **III-b2**:

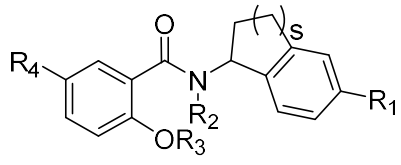

(**III-b**),

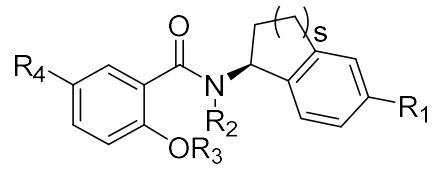

(**III-b1**),

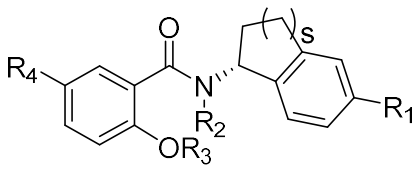

(**III-b2**),

or a pharmaceutically acceptable salt thereof.

[00020] In some examples, the compound of Formula **III** is a compound of Formula **III-c,** Formula **III-c1**, or Formula **III-c2**:


(**III-c**),


(**III-c1**),


(**III-c2**),

or a pharmaceutically acceptable salt thereof.

[00021] In one example, the present disclosure provides a method of treating neurological disease or disorder, wherein the method comprises administering to a subject in need thereof a compound disclosed herein (e.g., compound of Formula (I-I) or (I), (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-b1), (III-b2), (III-c), (III-c1), (III-c2))) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of Formula (I-I) or (I), (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-

b1), (III-b2), (III-c), (III-c1), (III-c2))), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient).

[00022] In another example, the present disclosure provides a method of treating a disease or condition associated with excessive neuronal excitability, wherein the method comprises administering to a subject in need thereof a compound disclosed herein (e.g., compound of Formula (I-I) or (I), (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-b1), (III-b2), (III-c), (III-c1), (III-c2))) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of Formula (I-I) or (I), (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-b1), (III-b2), (III-c), (III-c1), (III-c2))), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient).

[00023] In another example, the present disclosure provides a method of treating a disease or condition associated with a gain-of-function mutation of a gene (e.g. KCNT1), wherein the method comprises administering to a subject in need thereof a compound disclosed herein (e.g., a compound of Formula (I-I) or (I) (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-b1), (III-b2), (III-c), (III-c1), (III-c2))) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of Formula (I-I) or (I), (e.g., (I-Ia), (I-Ia1), (I-Ib), (I-Ib1), (I-Ic), (I-Ic1), (I-a), (I-a1), (I-b), (I-b1), (I-c), (I-c1), (I-d), or (I-d1)), a compound of Formula (II), (e.g., (II-a), (II-a1), (II-a2), (II-b), (II-b1), (II-b2), (II-c), (II-c1), (II-c2)), or a compound of Formula (III), (e.g., (III-a), (III-a1), (III-a2), (III-b), (III-b1), (III-b2), (III-c), (III-c1), (III-c2))), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient).

[00023a] In one aspect, the present disclosure refers to the use of a pharmacentical composition disclosed herein, in the manufacture of a medicament for treating a neurological disease or disorder, a disease or condition associated with excessive neuronal excitability, or a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1).

[00024] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is epilepsy, an epilepsy syndrome, or an encephalopathy.

[00025] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a genetic or pediatric epilepsy or a genetic or pediatric epilepsy syndrome.

[00026] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a cardiac dysfunction.

[00027] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, Lennox Gastaut syndrome, seizures (e.g., Generalized tonic clonic seizures, Asymmetric Tonic Seizures), leukodystrophy, leukoencephalopathy, intellectual disability, Multifocal Epilepsy, Drug resistant epilepsy, Temporal lobe epilepsy, cerebellar ataxia).

[00028] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of cardiac arrhythmia, sudden unexpected death in epilepsy, Brugada syndrome, and myocardial infarction.

[00029] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from pain and related conditions (e.g. neuropathic pain, acute/chronic pain, migraine, etc).

[00030] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a muscle disorder (e.g. myotonia, neuromyotonia, cramp muscle spasms, spasticity).

[00031] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from itch and pruritis, ataxia and cerebellar ataxias.

[00032] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia).

[00033] In some examples, the neurological disease or disorder or the disease or condition associated with excessive neuronal excitability and/or a gain-of-function mutation in a gene (e.g., KCNT1) is selected from the group consisting of learning disorders, Fragile X, neuronal plasticity, and autism spectrum disorders.

[00034] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

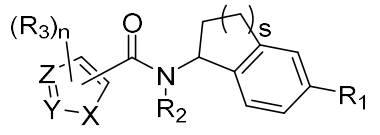
[00035] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

DETAILED DESCRIPTION OF THE INVENTION

[00036] As generally described herein, the present invention provides compounds and compositions useful for preventing and/or treating a disease, disorder, or condition described herein, e.g., a disease, disorder, or condition associated with excessive neuronal excitability, and/or a disease, disorder, or condition associated with gain-of-function mutations in KCNT1. Exemplary diseases, disorders, or conditions include epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, and Lennox Gastaut syndrome, seizures, leukodystrophy,

CLAIMS

1. A pharmaceutical composition comprising a compound of Formula **I-I**:



(I-I),

or a pharmaceutically acceptable salt thereof, wherein

X is selected from the group consisting of NH, O, and S, wherein the hydrogen of NH may be substituted with R_3;

Y is selected from N and CH, wherein the hydrogen of CH may be substituted with R_3;

Z is selected from N and CH, wherein the hydrogen of CH may be substituted with R_3, or Z is C when Z is substituted with the –C(O)N(R_2)- moiety;

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

each R_3 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-7}cycloalkyl, 3-7 membered heterocyclyl, -$S(O)_2NR_4R_5$, -$NR_4S(O)R_6$, -$C(O)NR_4R_5$, -$S(O)_2R_6$, and -O-R_6, wherein C_{1-6}alkyl is optionally substituted with one or more substituents independently selected from halogen, -NR_4R_5, and -$S(O)_2R_6$;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

R_4 and R_5 are each independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with oxo; or R_4 and R_5 may be taken together with the nitrogen to which R_4 and R_5 are attached to form a 4-7 membered heterocyclyl optionally substituted with one or more substituents independently selected from halogen, -OH, C_{1-6}alkyl, and C_{1-6}heteroalkyl;

each R_6 is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, phenyl, and benzyl; and

s is 1 or 2;

and a pharmaceutically acceptable excipient.

2. The pharmaceutical composition of claim 1, wherein x is NH, O, or S.

3. The pharmaceutical composition of claim 1 or 2, wherein Y is N or CH.

4. The pharmaceutical composition of any one of claims 1-3, wherein Z is N or CH.

5. The pharmaceutical composition of any one of claims 1-4, wherein R_1 is selected from the group consisting of -Cl, -F, and -CF_3.

6. The pharmaceutical composition of any one of claims 1-5, wherein each R_3 is selected from the group consisting of -Cl, methyl, methyl substituted with $-NR_4R_5$ or $-S(O)_2R_6$, methoxymethyl, trifluoromethyl, ethyl, cyclopropyl, cyclohexyl, $-S(O)_2R_6$, $-C(O)NR_4R_5$, and $-S(O)_2NR_4R_5$.

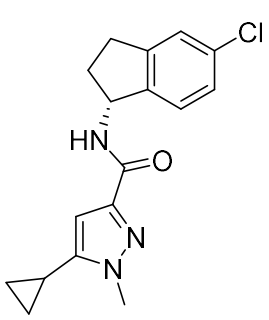
7. The pharmaceutical composition of any one of claims 1-6, wherein n is 1 or 2.

8. The pharmaceutical composition of any one of claims 1-7, wherein each of R_4 and R_5 are independently selected from the group consisting of hydrogen, methyl, ethyl, cyclopropyl, and $-C(O)CH_3$ or wherein R_4 and R_5 are taken together with the nitrogen to which R_4 and R_5 are attached to form a 4-6 membered heterocyclyl optionally substituted with -OH, methyl, or $-OCH_3$.

9. The pharmaceutical composition of any one of claims 1-8, wherein R_6 is selected from the group consisting of methyl, ethyl, methoxyethyl, and cyclopropyl.

10. The pharmaceutical composition of any one of claims 1-9, wherein s is 1 or 2.

11. The pharmaceutical composition of claim 1, wherein the compound is selected from the group consisting of: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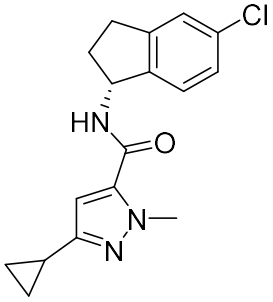
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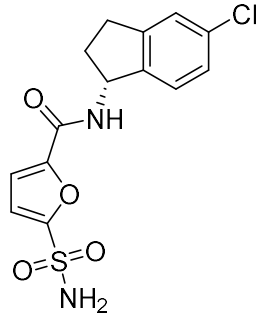
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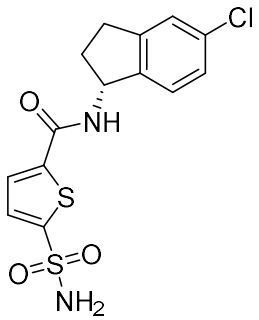
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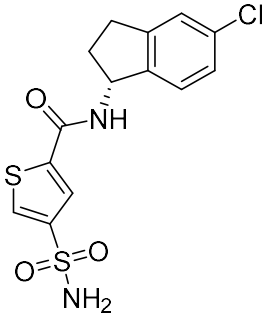
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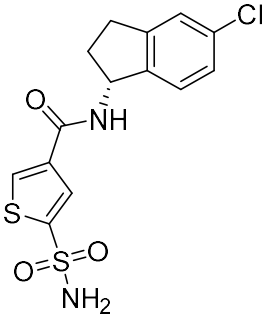
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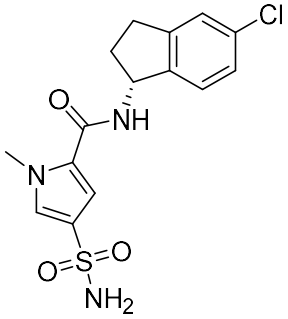
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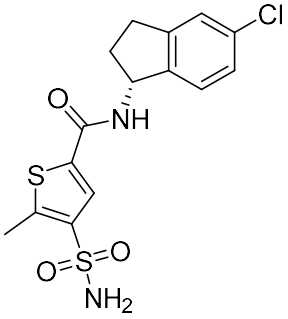
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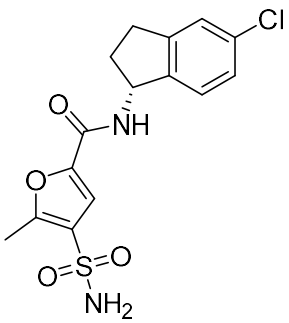
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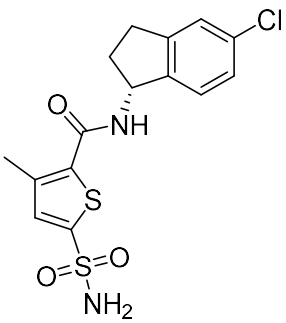
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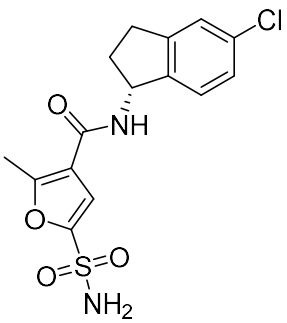
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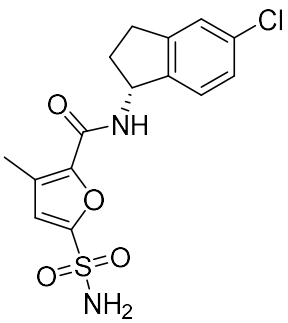
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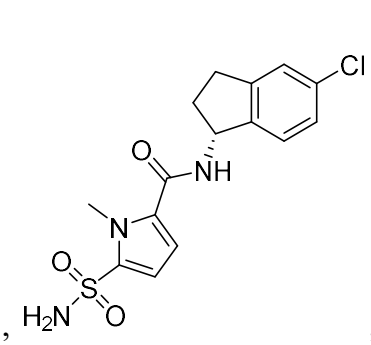
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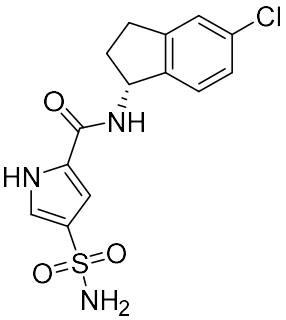
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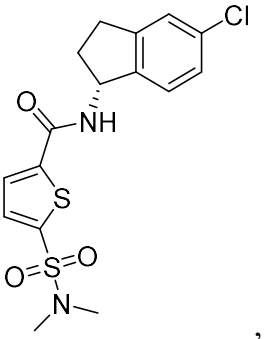
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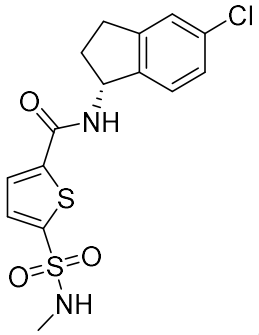
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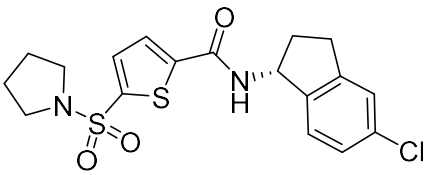
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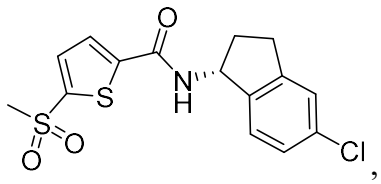
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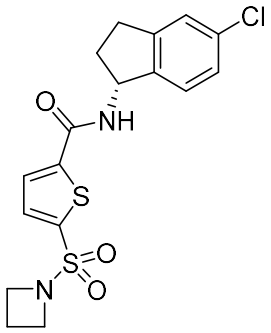
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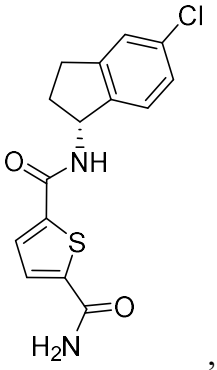
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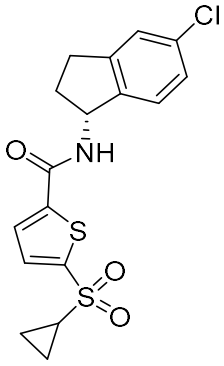
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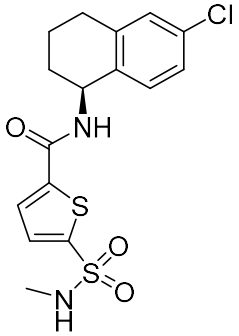
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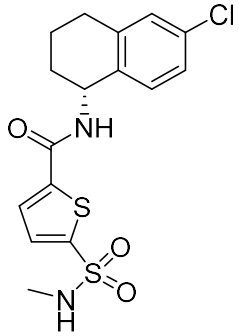
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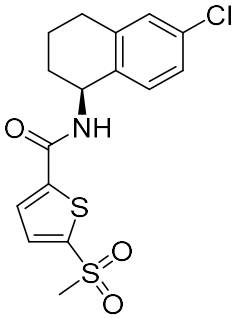
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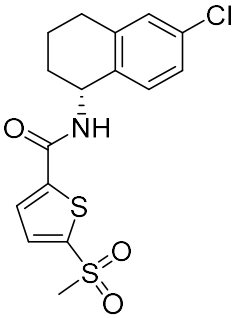
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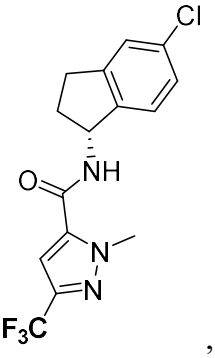
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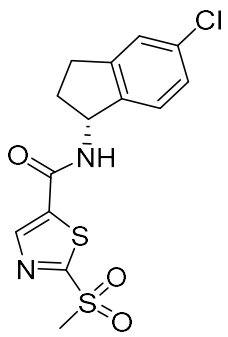
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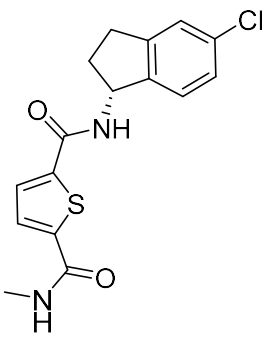
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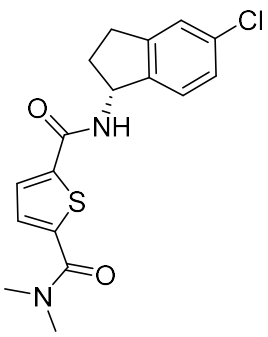
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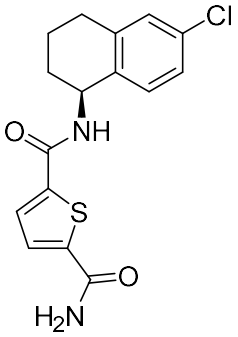
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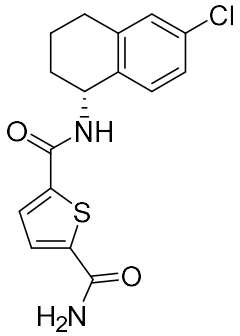
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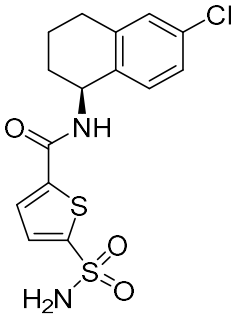
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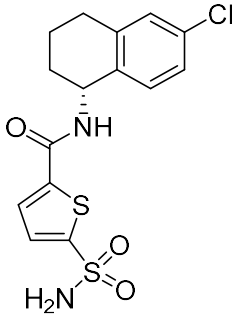
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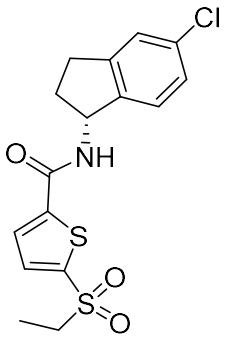
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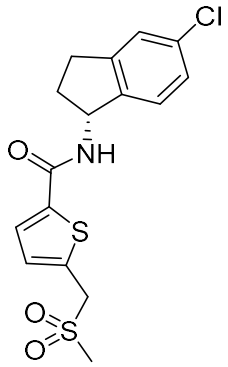
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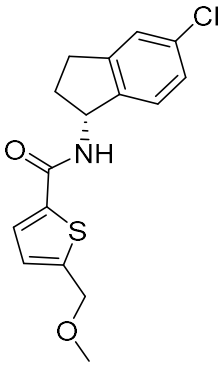
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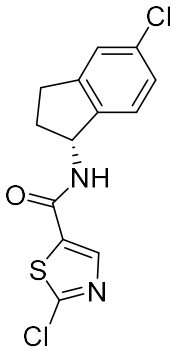
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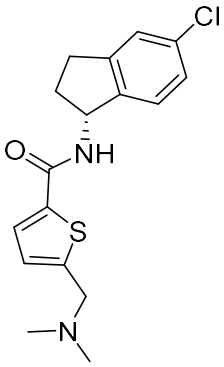
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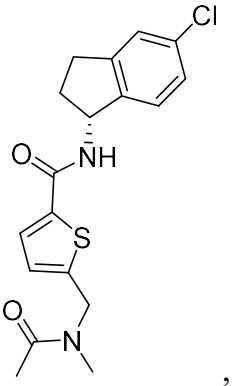
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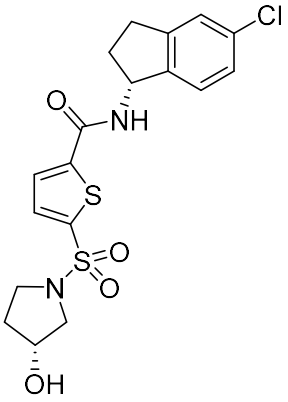
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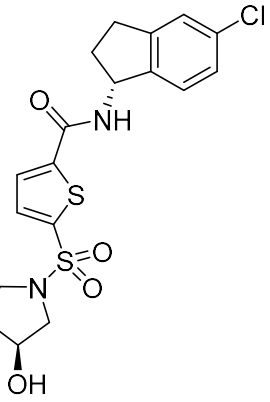
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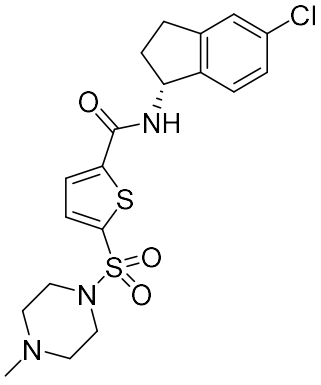
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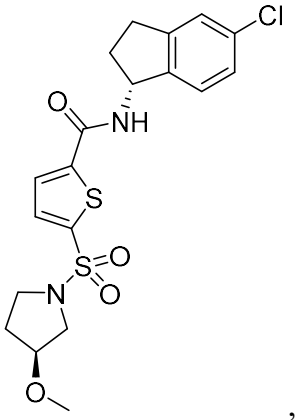
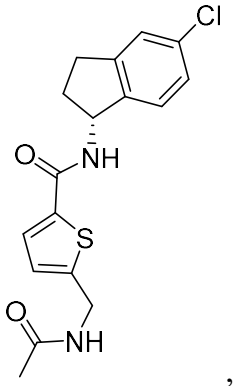
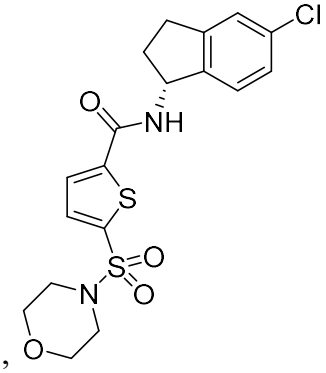
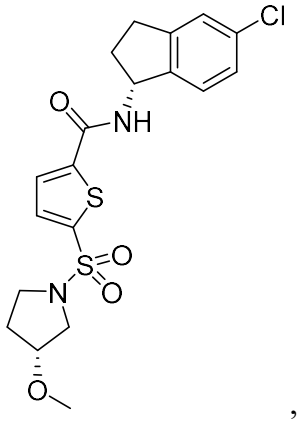
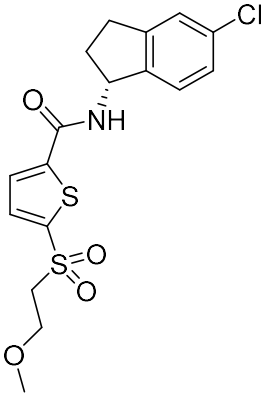






and , or a pharmaceutically acceptable salt thereof.

12. Use of a pharmacentical composition of any one of claims 1-11, in the manufacture of a medicament for treating a neurological disease or disorder, a disease or condition associated with excessive neuronal excitability, or a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1).

13. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is epilepsy, an epilepsy syndrome, or an encephalopathy.

14. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a genetic or pediatric epilepsy or a genetic or pediatric epilepsy syndrome.

15. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a cardiac dysfunction.

16. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition

associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, Lennox Gastaut syndrome, seizures (e.g., Generalized tonic clonic seizures, Asymmetric Tonic Seizures), leukodystrophy, leukoencephalopathy, intellectual disability, Multifocal Epilepsy, Drug resistant epilepsy, Temporal lobe epilepsy, or cerebellar ataxia).

17. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of cardiac arrhythmia, sudden unexpected death in epilepsy, Brugada syndrome, and myocardial infarction.

18. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from pain and related conditions (e.g. neuropathic pain, acute/chronic pain, migraine).

19. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a muscle disorder (e.g. myotonia, neuromyotonia, cramp muscle spasms, spasticity).

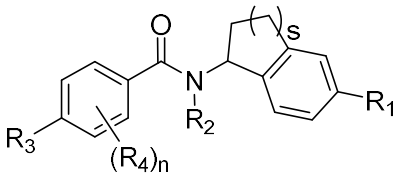
20. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from itch and pruritis, ataxia and cerebellar ataxias.

21. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia).

22. The use of claim 12, wherein the neurological disease or disorder or the disease or condition associated with excessive neuronal excitability and/or a gain-of-function mutation in a gene (e.g., KCNT1) is selected from the group consisting of learning disorders, Fragile X, neuronal plasticity, and autism spectrum disorders.

23. The use of claim 12, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

24. A pharmaceutical composition comprising a compound of Formula **II**:



(**II**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

R_3 is independently selected from the group consisting of halogen, C_{1-6}alkoxy, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$C(O)NR_5R_6$, -$NR_7S(O)_2C_{1-6}$alkyl, -$NR_7S(O)_2C_{3-7}$ cycloalkyl, -$NR_7S(O)_2NR_5R_6$, -NR_9R_{10}, -$S(O)_2$-C_{3-6}cycloalkyl, -$S(O)_2$-NR_5R_6, -$S(O)_2$-C_{1-6}alkoxy, and -$S(O)_2$-C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halogen or C_{1-6}alkoxy;

each R_4 is independently selected from the group consisting of C_{1-6}alkyl, halogen, and -OH; wherein R_4 is substituted at the carbon adjacent to R_3 when R_4 is -OH;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

R_5, R_6, R_9, and R_{10} are each independently hydrogen or C_{1-6}alkyl;

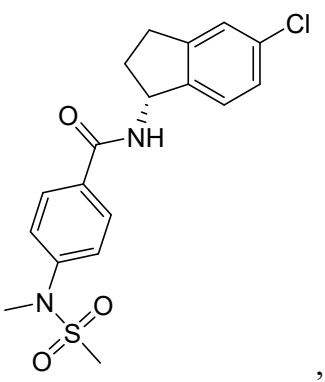
each R_7 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and 3-7 membered heterocyclyl, wherein the C_{1-6}alkyl is optionally substituted with one or

more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OH, -NR_5R_6, and -$C(O)NR_5R_6$; and

s is 1 or 2;

and a pharmaceutically acceptable excipient.

25. The pharmaceutical composition of claim 24, wherein the compound is selected from the group consisting of: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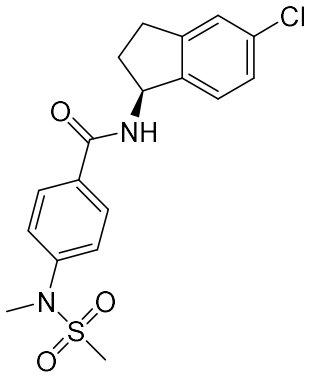
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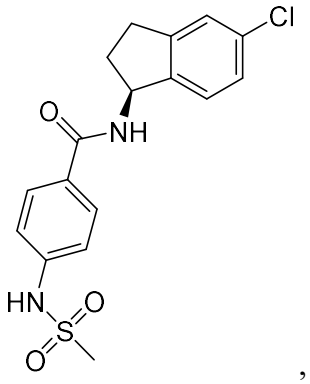
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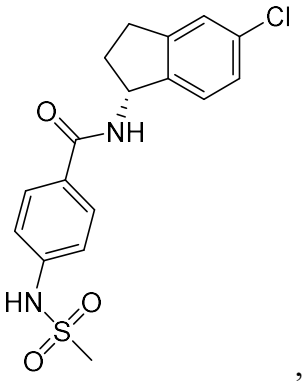
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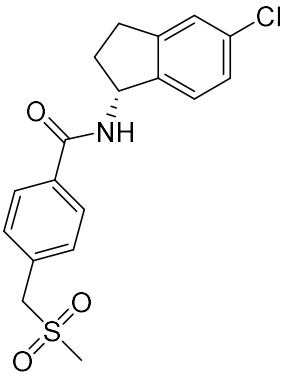
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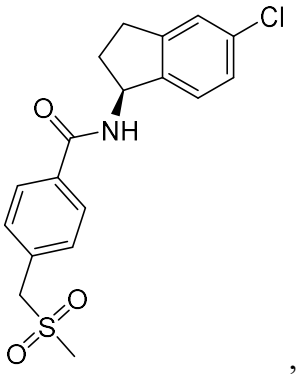
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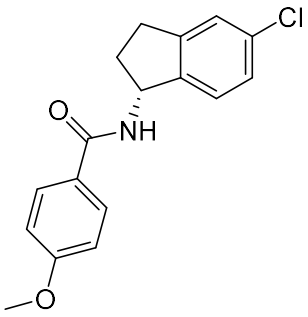
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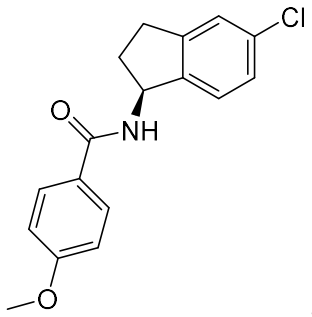
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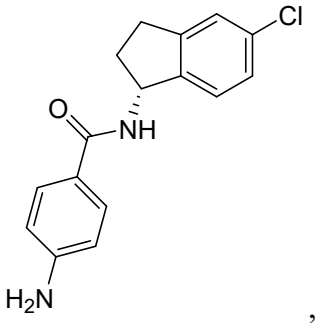
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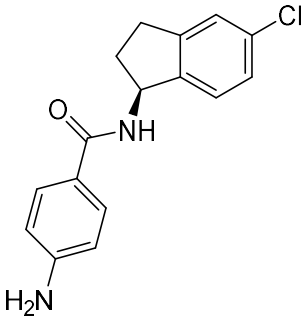
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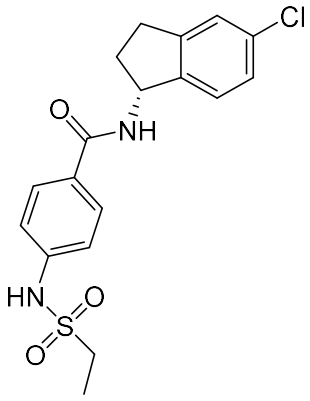
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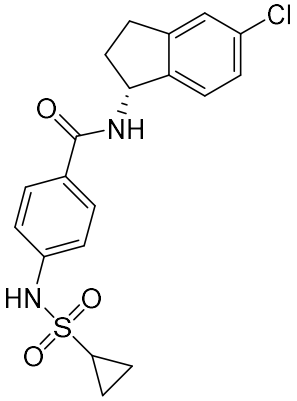
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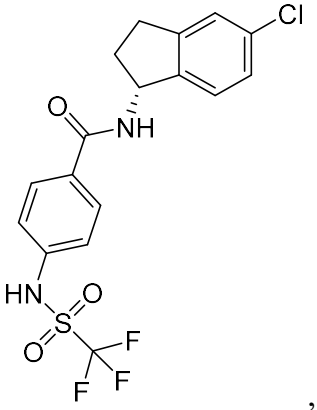
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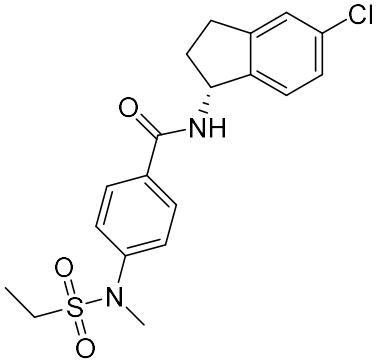
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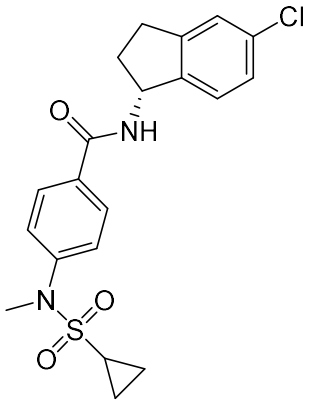
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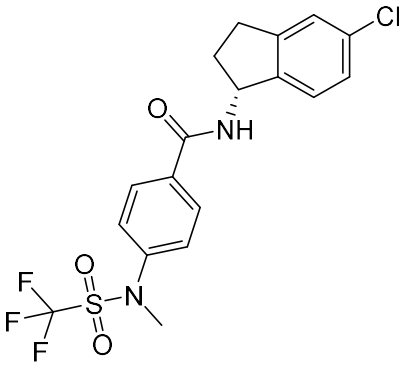
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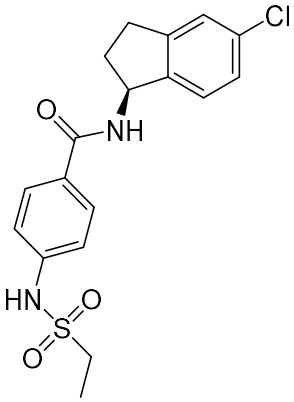
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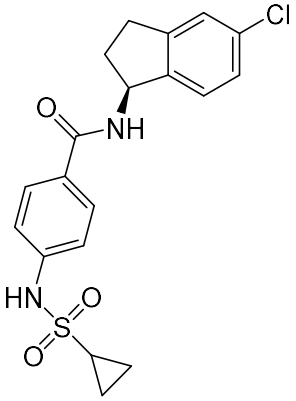
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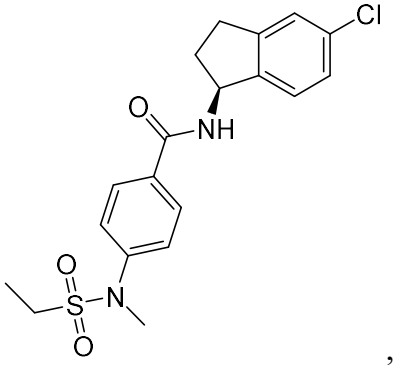
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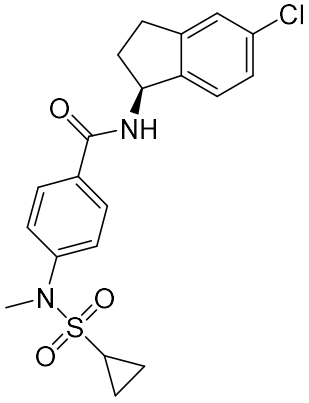
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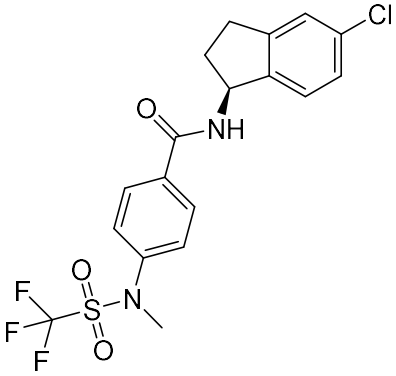
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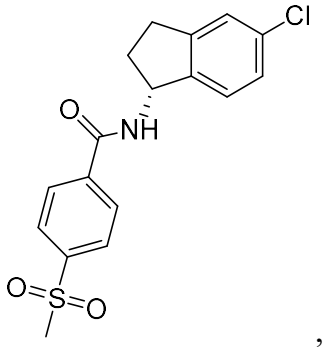
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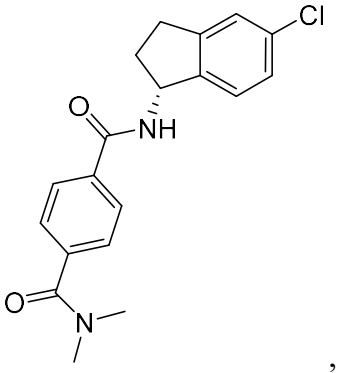
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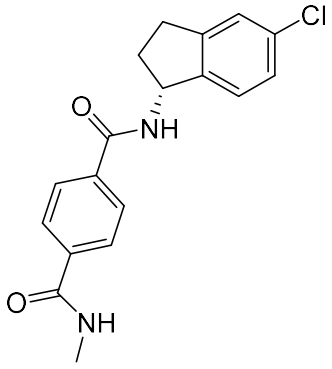
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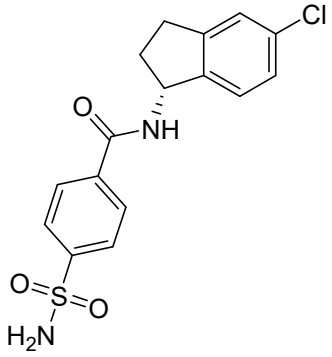
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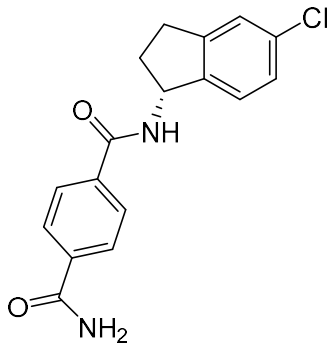
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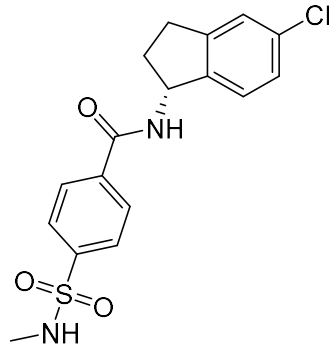
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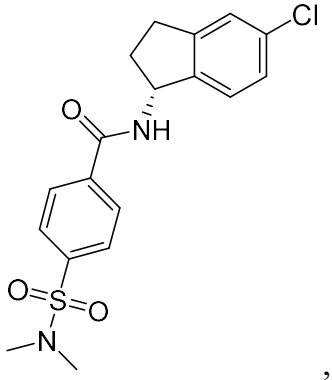
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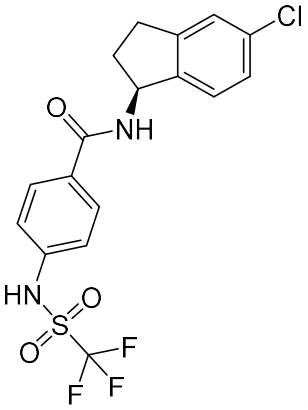
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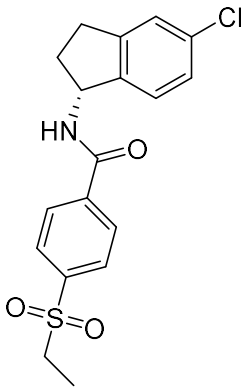
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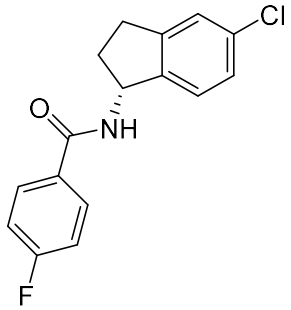
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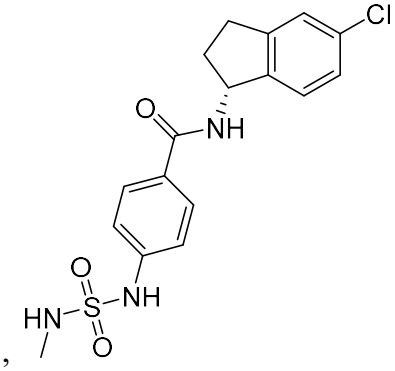
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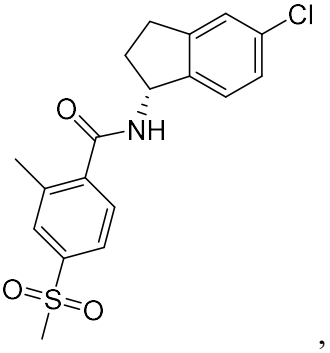
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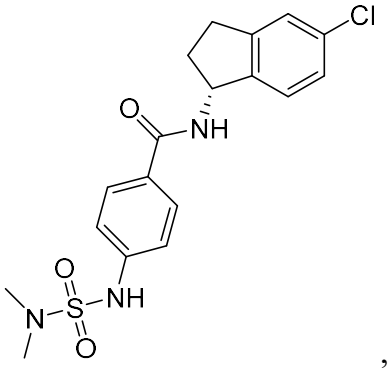
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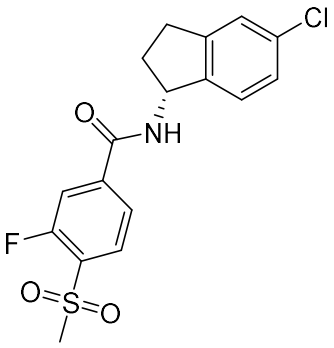
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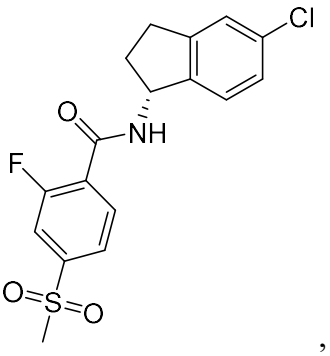
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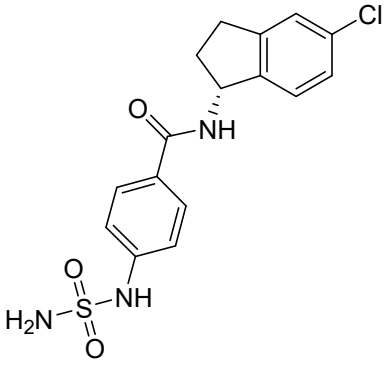
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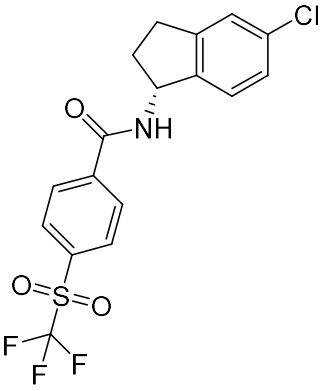
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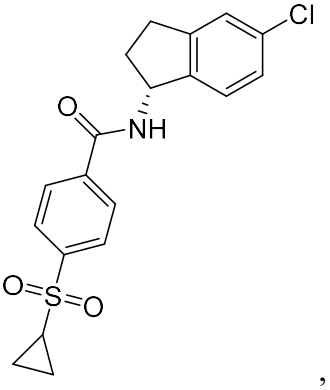
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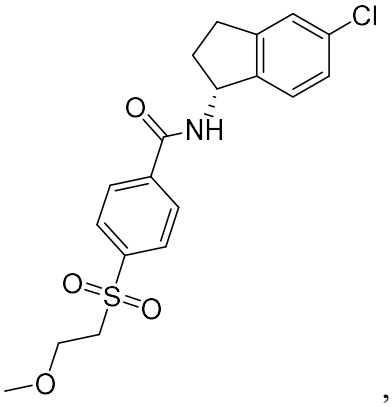
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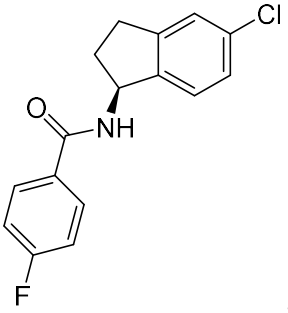
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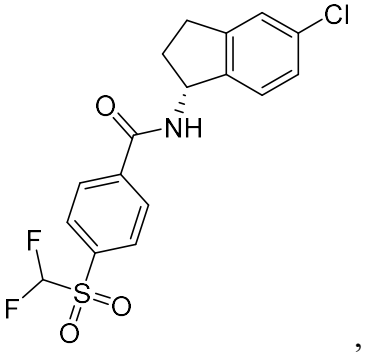
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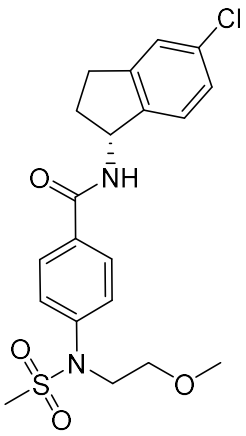
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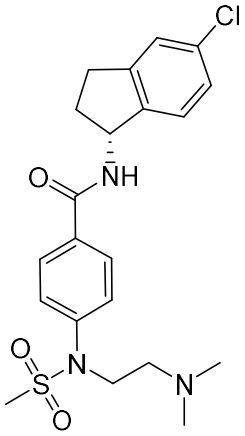
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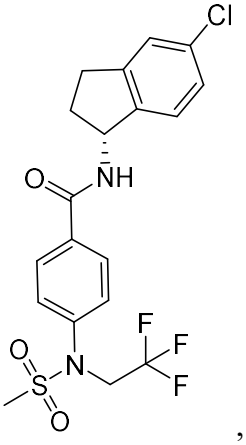
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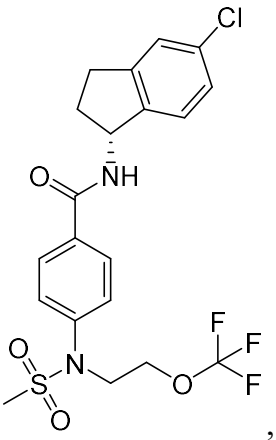
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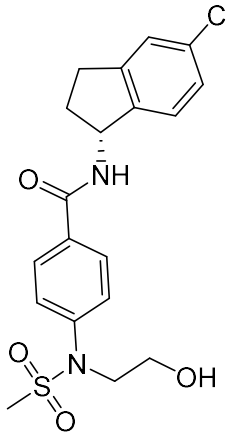
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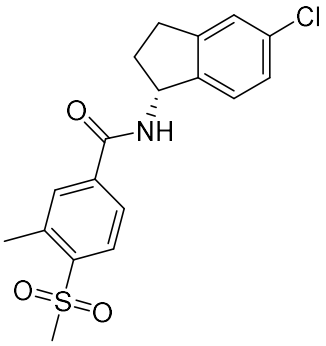
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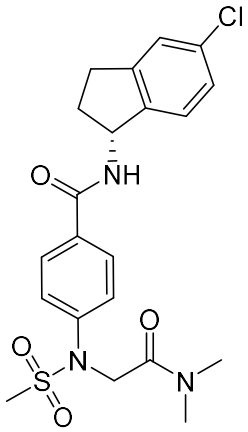
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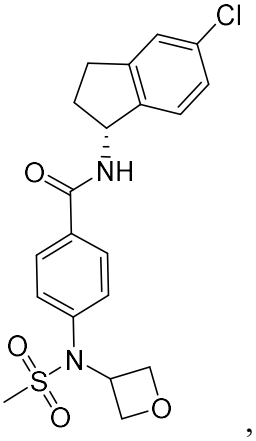
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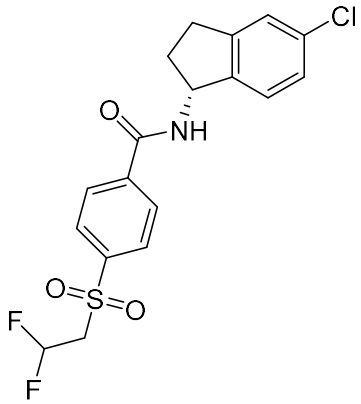
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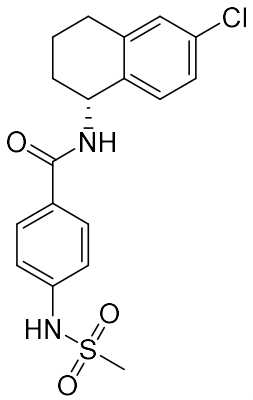
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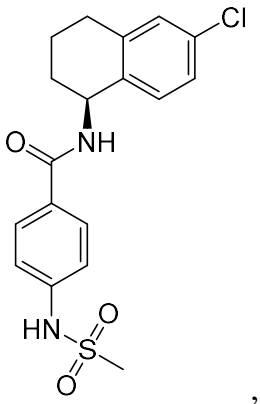
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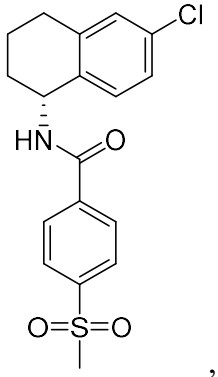
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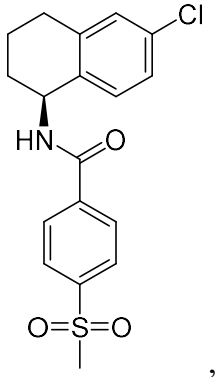
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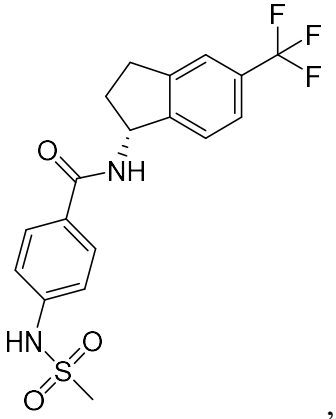
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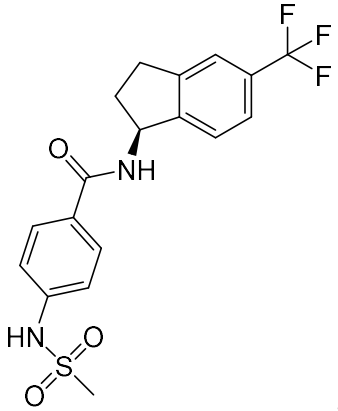
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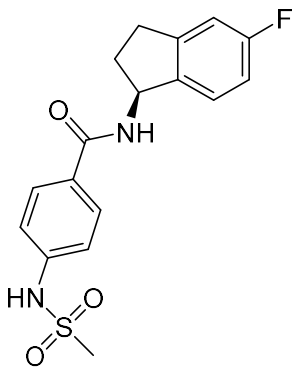
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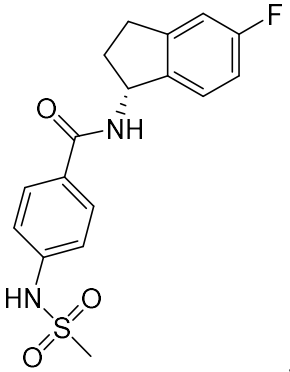

, or a pharmaceutically acceptable salt thereof.

26. Use of a pharmaceutical composition of claim 24 or 25, in the manufacture of a medicament for treating a neurological disease or disorder, a disease or condition associated with excessive neuronal excitability, or a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1).

27. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is epilepsy, an epilepsy syndrome, or an encephalopathy.

28. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a genetic or pediatric epilepsy or a genetic or pediatric epilepsy syndrome.

29. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a cardiac dysfunction.

30. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, Lennox Gastaut syndrome, seizures (e.g., Generalized tonic clonic seizures, Asymmetric Tonic Seizures), leukodystrophy, leukoencephalopathy, intellectual disability, Multifocal Epilepsy, Drug resistant epilepsy, Temporal lobe epilepsy, or cerebellar ataxia).

31. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of cardiac arrhythmia, sudden unexpected death in epilepsy, Brugada syndrome, and myocardial infarction.

32. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from pain and related conditions (e.g. neuropathic pain, acute/chronic pain, migraine).

33. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a muscle disorder (e.g. myotonia, neuromyotonia, cramp muscle spasms, spasticity).

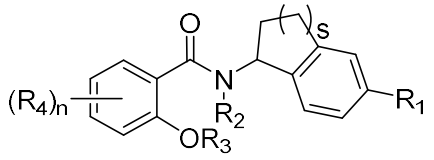
34. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from itch and pruritis, ataxia and cerebellar ataxias.

35. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia).

36. The use of claim 26, wherein the neurological disease or disorder or the disease or condition associated with excessive neuronal excitability and/or a gain-of-function mutation in a gene (e.g., KCNT1) is selected from the group consisting of learning disorders, Fragile X, neuronal plasticity, and autism spectrum disorders.

37. The use of claim 26, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

38. A pharmaceutical composition comprising a compound of Formula **III**:



(**III**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of -Cl, -F, and C_{1-6}alkyl substituted with one or more substituents independently selected from -Cl and -F;

R_2 is hydrogen;

R_3 is hydrogen;

R_4 is each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-NR_7S(O)_2C_{1-6}$alkyl, and $-NR_8C(O)-C_{1-6}$alkyl;

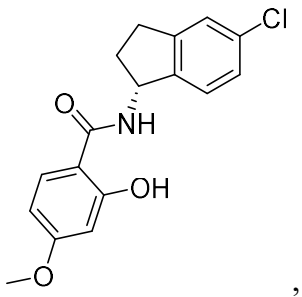
n is selected from the group consisting of 0, 1, 2, 3, and 4;

R_7 and R_8 are each independently hydrogen or C_{1-6}alkyl; and

s is 1 or 2;

and a pharmaceutically acceptable excipient.

39. The pharmaceutical composition of claim 38, wherein the compound is selected from the group consisting of:



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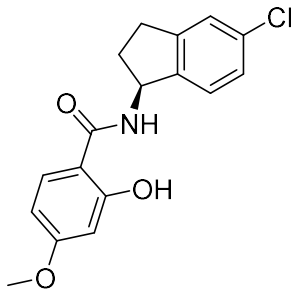

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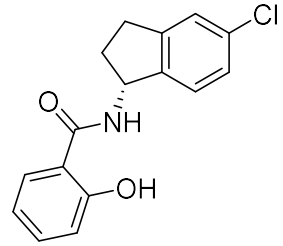

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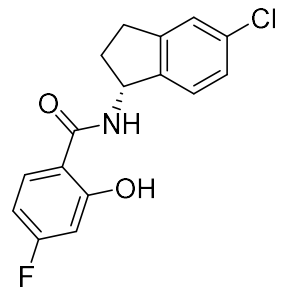

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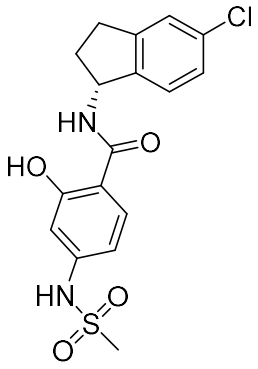

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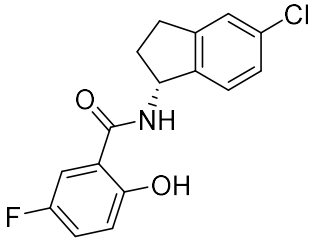

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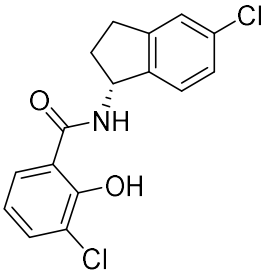

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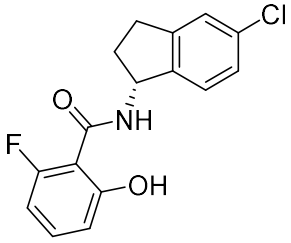

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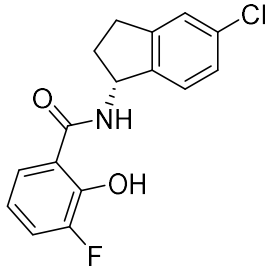

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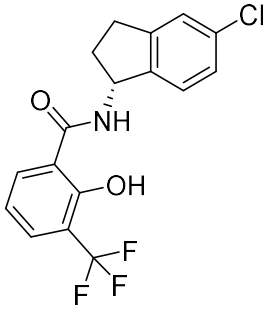

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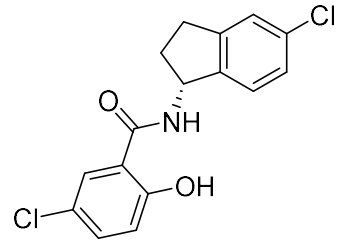

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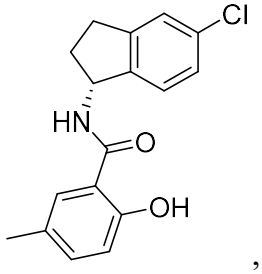

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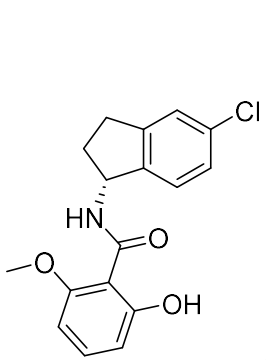

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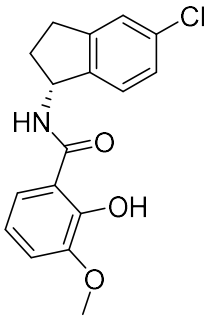

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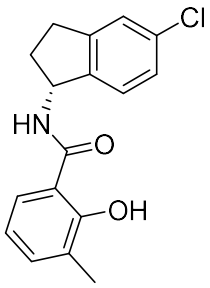

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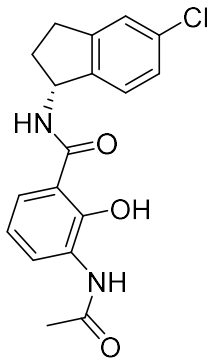

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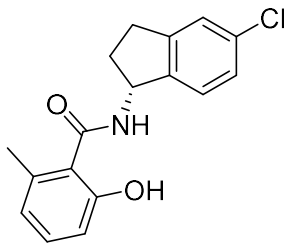

, or a pharmaceutically acceptable salt thereof.

40. Use of a pharmaceutical composition of claim 38 or 39, in the manufacture of a medicament for treating a neurological disease or disorder, a disease or condition associated with excessive neuronal excitability, or a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1).

41. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is epilepsy, an epilepsy syndrome, or an encephalopathy.

42. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a genetic or pediatric epilepsy or a genetic or pediatric epilepsy syndrome.

43. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a cardiac dysfunction.

44. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal

epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, Lennox Gastaut syndrome, seizures (e.g., Generalized tonic clonic seizures, Asymmetric Tonic Seizures), leukodystrophy, leukoencephalopathy, intellectual disability, Multifocal Epilepsy, Drug resistant epilepsy, Temporal lobe epilepsy, or cerebellar ataxia).

45. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of cardiac arrhythmia, sudden unexpected death in epilepsy, Brugada syndrome, and myocardial infarction.

46. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from pain and related conditions (e.g. neuropathic pain, acute/chronic pain, migraine).

47. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is a muscle disorder (e.g. myotonia, neuromyotonia, cramp muscle spasms, spasticity).

48. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from itch and pruritis, ataxia and cerebellar ataxias.

49. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia).

50. The use of claim 40, wherein the neurological disease or disorder or the disease or condition associated with excessive neuronal excitability and/or a gain-of-function mutation in a gene (e.g., KCNT1) is selected from the group consisting of learning disorders, Fragile X, neuronal plasticity, and autism spectrum disorders.

51. The use of claim 40, wherein the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from the group consisting of epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A

mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.