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 62/842,849 filed May 3, 2019 and U.S. Provisional Patent Application Number 62/982,864 filed February 28, 2020, the contents of each of which are incorporated herein by reference in their entirety.

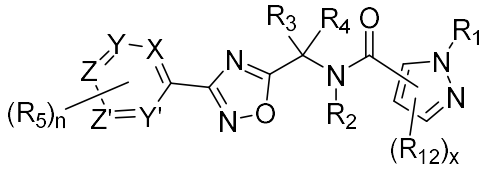
BACKGROUND

[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.

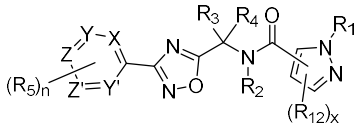
[0004] In one example, the present disclosure features a pharmaceutical composition comprising a compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein, and a pharmaceutically acceptable excipient.

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



(I),

or a pharmaceutically acceptable salt thereof, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, $-C(O)OR_8$, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, $-S(O)_2-C_{1-6}$alkyl, C_{1-6}alkylene-$S(O)_2-C_{1-6}$alkyl, $-S(O)_2-N(R_9)_2$, $-OC(O)C_{1-6}$alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, $-N(R_9)_2$, $-NR_9-SO_2-C_{1-6}$alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, $-C(O)OR_8$, $-C(O)N(R_9)_2$,-$NR_{10}C(O)-R_{11}$, -CN, $-S(O)_2-C_{1-6}$alkyl, $-S(O)_2-N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and $-N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

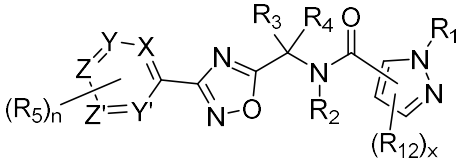
each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N;

and a pharmaceutically acceptable excipient.

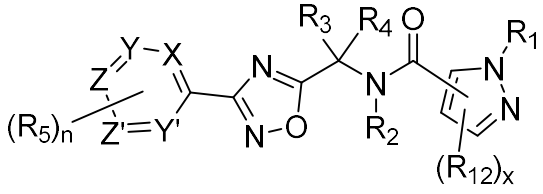
[0005] In another example, the present disclosure features a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0005a] In one aspect, the present disclosure refers to a compound of Formula **II**:



(**II**),

or a pharmaceutically acceptable salt thereof, wherein

one or two selected from X, Y, Z, Y', and Z' are N, and the others are CH, wherein the hydrogen of CH may be substituted with R_5;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy optionally substituted with C_{3-7}cycloalkyl, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, -$N(R_9)_2$, -$C(O)OR_8$, -$C(O)N(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -$C(O)OR_8$, -$C(O)N(R_9)_2$,-$NR_{10}C(O)$-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, and C_{3-10}cycloalkyl;

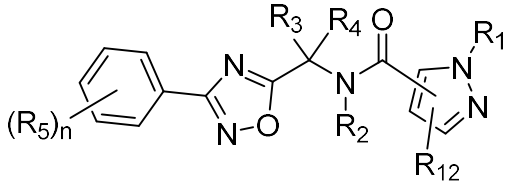
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to

form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl; and

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl.

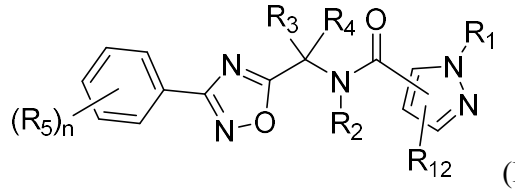
[0006] In another example, the present disclosure features a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0006a] In one aspect, the present disclosure refers to a compound of Formula **III**:



(**III**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl is optionally substituted with one or more halogen or C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, and phenyl, wherein the C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, or phenyl is optionally substituted with one or more substituents each independently selected from halogen and C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -$C(O)OR_8$, -$C(O)N(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, -$OC(O)C_{1-6}$alkyl, and -O-C_{1-3}cycloalkyl optionally substituted with one or more halogen;

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -$C(O)OR_8$, -$C(O)N(R_9)_2$,-$NR_{10}C(O)$-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

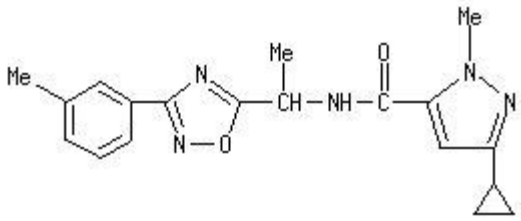
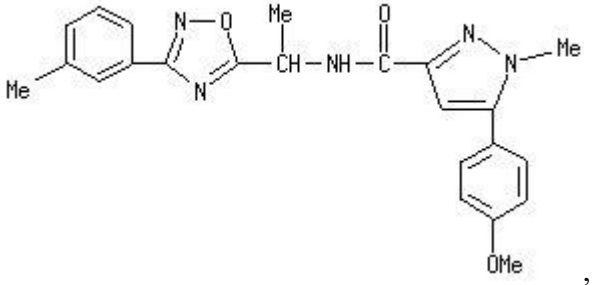
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

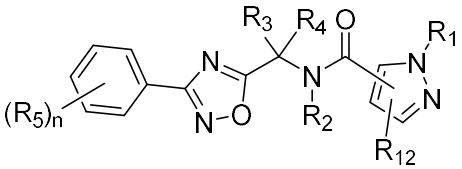
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

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

wherein the compound is not:

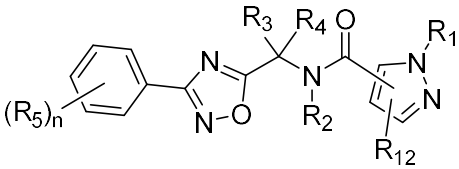

,

, or a pharmaceutically acceptable salt thereof.

[0007] In another example, the present disclosure features a compound of Formula (IV):


(IV),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0007a] In one aspect, the present disclosure refers to a compound of Formula **IV**:


(**IV**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of C_{1-6}alkyl, and C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6}alkoxy;

R_{12} is C_{1-6}alkyl optionally substituted with one or more halogen or C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -C(O)OR_8, -C(O)N(R_9)$_2$, -C_{1-6}alkylene-CN, -CN, -S(O)$_2$-C_{1-6}alkyl, C_{1-6}alkylene-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$- N(R_9)$_2$, -OC(O)C_{1-6}alkyl, and -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen;

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)N(R_9)$_2$,-NR_{10}C(O)-R_{11}, -CN, -S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$- N(R_9)$_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -N(R_9)$_2$;

R_8 is hydrogen or C_{1-6}alkyl;

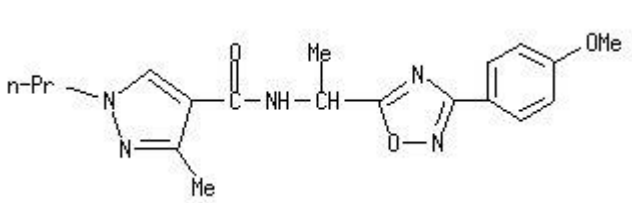
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents selected from halogen and -OH;

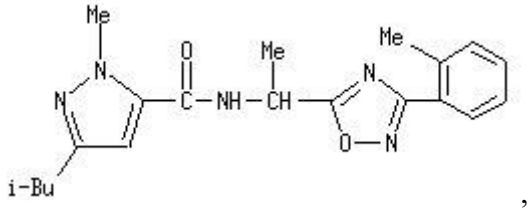
each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

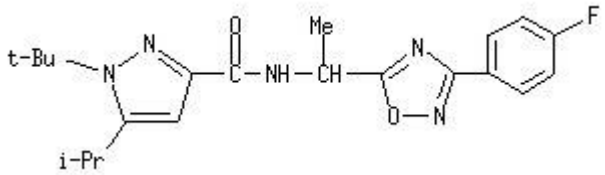
n is selected from the group consisting of 0, 1, 2, and 3;

wherein the compound is not:



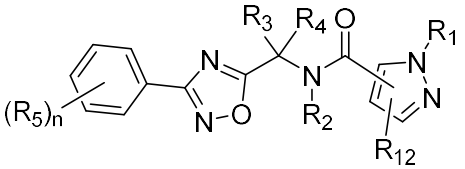
,


,



, or a pharmaceutically acceptable salt thereof.

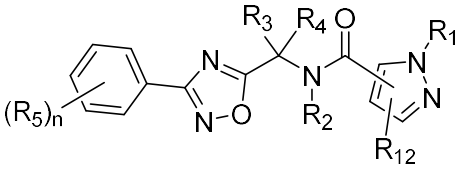
[0008] In another example, the present disclosure features a compound of Formula (V):



(V),

Or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0008a] In one aspect, the present disclosure refers to a compound of Formula **V**:



(**V**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is phenyl or 3-10 membered heteroaryl, wherein the phenyl or 3-10 membered heteroaryl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6}alkoxy,

R_{12} is selected from the group consisting of C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from halogen and C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -$C(O)OR_8$, -$C(O)N(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, -$OC(O)C_{1-6}$alkyl, and -O-C_{3-10}cycloalkyl;

R_7 is selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -O-(C_{1-6}alkylene)-phenyl, C_{3-7}cycloalkyl, -$C(O)OR_8$, -$C(O)N(R_9)_2$,-$NR_{10}C(O)$-R_{11}, -CN, -$S(O)_z$-C_{1-6}alkyl, -$S(O)_z$-$N(R_9)_2$, 3-7 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with

one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -N(R_9)$_2$;

R_8 is hydrogen or C_{1-6}alkyl;

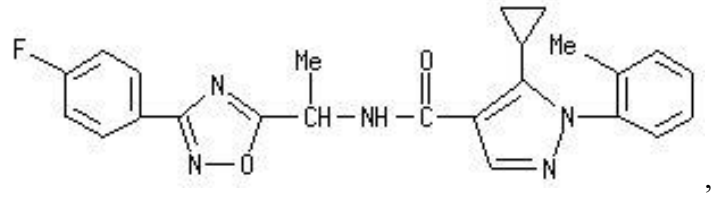
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

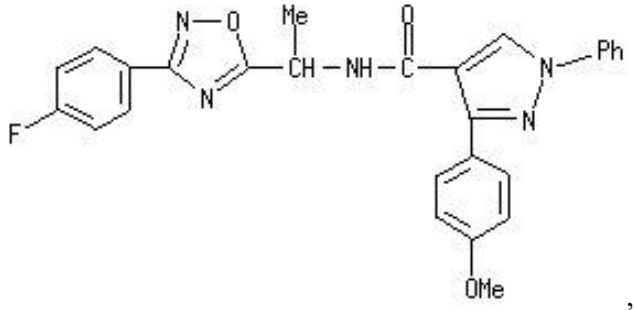
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

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

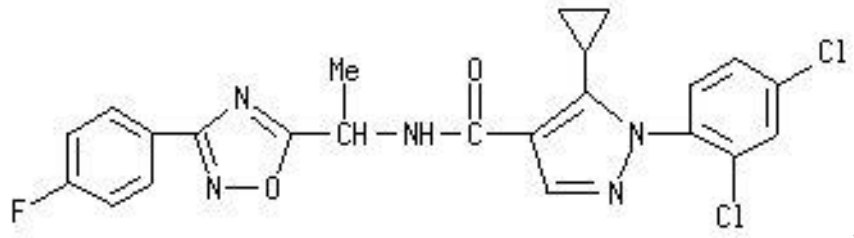
wherein the compound is not:



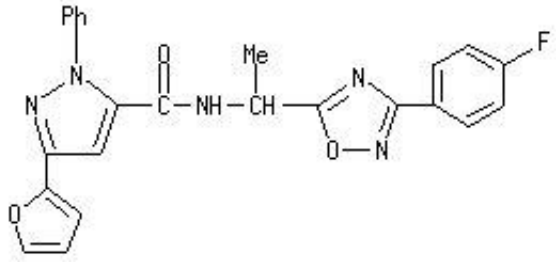
,



,

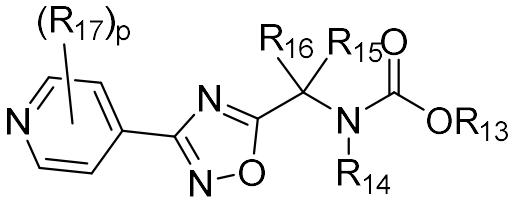


,



, or a pharmaceutically acceptable salt thereof.

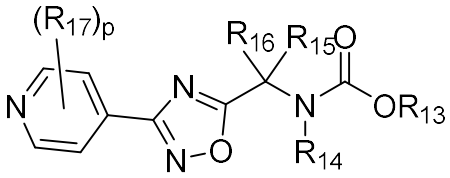
[0009] In another example, the present disclosure features a compound of Formula (VI):



(VI),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0009a] In one aspect, the present disclosure refers to a compound of Formula **VI**:



(**VI**),

or a pharmaceutically acceptable salt thereof, wherein

R_{13} is $C_{1\text{-}6}$alkyl or $C_{3\text{-}10}$cycloalkyl, wherein the $C_{1\text{-}6}$alkyl or $C_{3\text{-}10}$cycloalkyl is optionally substituted with phenyl;

R_{14} is hydrogen;

R_{15} is $C_{1\text{-}6}$alkyl or hydrogen;

R_{16} is $C_{1\text{-}6}$alkyl optionally substituted with one or more halogen, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$ cycloalkyl, or phenyl;

each R_{17} is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkylene-$N(R_{20})_2$, $C_{1\text{-}6}$alkylene-O-$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy optionally substituted with $C_{3\text{-}7}$cycloalkyl, $C_{1\text{-}6}$haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or $C_{1\text{-}6}$alkoxy, 3-10 membered heteroaryl, -$C_{1\text{-}6}$alkylene-OH, $C_{1\text{-}6}$alkylene-$C_{1\text{-}6}$alkoxy, OH, -$N(R_{20})_2$, -C(O)OR_{19}, -C(O)$N(R_{20})_2$, -$C_{1\text{-}6}$alkylene-CN, -CN, -$S(O)_2$-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylene-$S(O)_2$-$C_{1\text{-}6}$alkyl, -$S(O)_2$- $N(R_{20})_2$, -OC(O)$C_{1\text{-}6}$alkyl, -O-$C_{3\text{-}10}$cycloalkyl optionally substituted with one or more halogen or $C_{1\text{-}6}$alkyl, and $C_{3\text{-}10}$cycloalkyl optionally substituted with one or more substituents selected from halogen, $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkoxy;

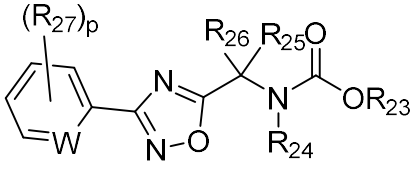
p is selected from the group consisting of 1, 2, and 3;

R_{19} is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, and $C_{3\text{-}10}$cycloalkyl;

each R_{20} is independently hydrogen or $C_{1\text{-}6}$alkyl; and

each R_{21} is independently hydrogen or $C_{1\text{-}6}$alkyl.

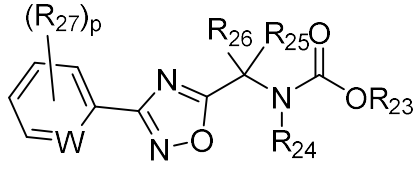
[00010] In another example, the present disclosure features a pharmaceutical composition comprising a compound of Formula (VII):



(VII),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein, and a pharmaceutically acceptable excipient.

[00010a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula **VII**:



(**VII**),

or a pharmaceutically acceptable salt thereof, wherein

W is N or CH;

R_{23} is $C_{1\text{-}6}$alkyl;

R_{24} is hydrogen;

R_{25} is $C_{1\text{-}6}$alkyl or hydrogen;

R_{26} is $C_{1\text{-}6}$alkyl optionally substituted with one or more halogen or $C_{1\text{-}6}$alkoxy;

each R_{27} is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, and $C_{1\text{-}6}$alkoxy; and

p is selected from the group consisting of 1, 2, and 3;

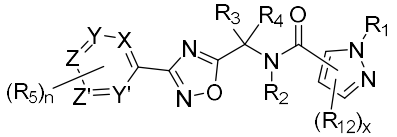
and a pharmaceutically acceptable excipient.

[00011] In another example, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a))) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00011a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00012] In another example, the present disclosure provides a method of treating a neurological disease or disorder, wherein the method comprises administering to a subject in need thereof a compound disclosed herein (e.g., a compound of formula (I), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-b)) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula (I), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-b)) or a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable excipient).

[00012a] In one aspect, the present disclosure refers to use of a compound of Formula **I**:



(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a neurological disease or disorder, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or

more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, $-C(O)OR_8$, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, $-S(O)_2-C_{1-6}$alkyl, C_{1-6}alkylene-$S(O)_2-C_{1-6}$alkyl, $-S(O)_2-N(R_9)_2$, $-OC(O)C_{1-6}$alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, $-N(R_9)_2$, $-NR_9-SO_2-C_{1-6}$alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, $-C(O)OR_8$, $-C(O)N(R_9)_2$,-$NR_{10}C(O)-R_{11}$, -CN, $-S(O)_2-C_{1-6}$alkyl, $-S(O)_2-N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and $-N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

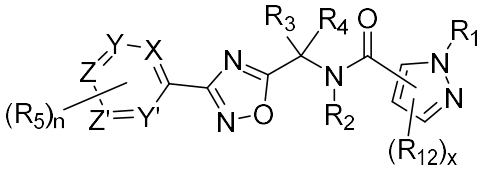
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

[00013] 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., a compound of formula (I), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-b)) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula (I), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-

b)) or a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable excipient).

[00013a] In one aspect, the present disclosure refers to use of a compound of Formula **I**:



(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with excessive neuronal excitability, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, -C(O)OR_8, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -$C(O)N(R_9)_2$,-$NR_{10}C(O)$-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

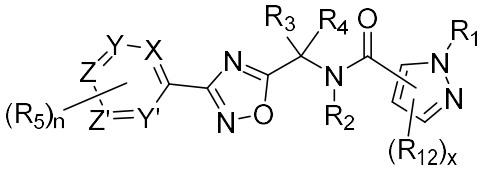
each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

[00014] 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), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-b)) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula ((I), (e.g., (I-I), (I-II), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (I-k), (I-l), (I-m), (I-n), (I-o), (I-p), (I-q), (I-r), or (I-s)), (II), (e.g., (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-k1), or (II-k2)), (III), (IV), (V), (VI), (e.g., (VI-a)), or (VII), (e.g., (VII-a) or (VII-b)) or a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable excipient).

[00014a] In one aspect, the present disclosure refers to use of a compound of Formula **I**:



(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1), wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, -C(O)OR_8, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, -S(O)$_2$-C_{1-6}alkyl, C_{1-6}alkylene-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-}

$_{10}$cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)$N(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

[00014b] In one aspect, the present disclosure refers to use of a compound disclosed herein, or a pharmaceutical 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).

[00015] 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.

[00016] 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.

[00017] 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.

[00018] 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).

[00019] 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.

[00020] 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).

[00021] 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).

[00022] 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.

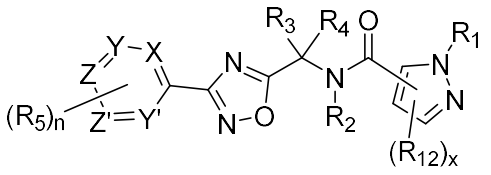
[00023] In some examples, the neurological disease or disorder, the disease or condition associated with excessive neuronal excitability, or the disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1) is selected from psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia).

[00024] 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.

[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 selected from the group consisting of epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A

CLAIMS

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



(I),

or a pharmaceutically acceptable salt thereof, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-}

$_{6}$haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, -C(O)OR_8, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -$C(O)N(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

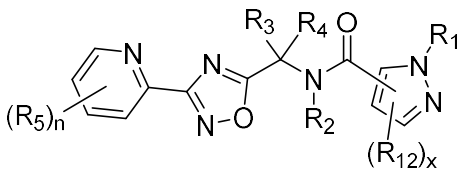
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N;

and a pharmaceutically acceptable excipient.

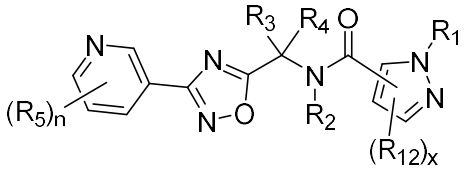
2. The pharmaceutical composition of claim 1, wherein one of X, Y, Z, Y', and Z' is N and the other four are CH.

3. The pharmaceutical composition of claim 1, wherein the compound is chosen from: a compound of Formula **I-a**:

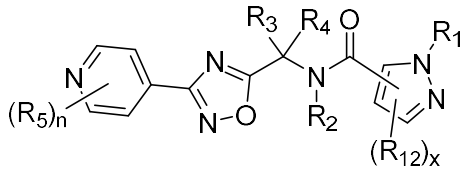


(**I-a**),

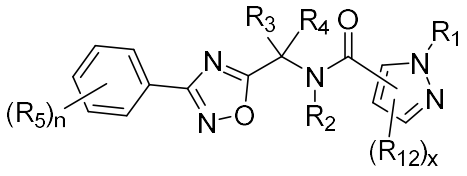
a compound of Formula **I-b**:


(**I-b**),

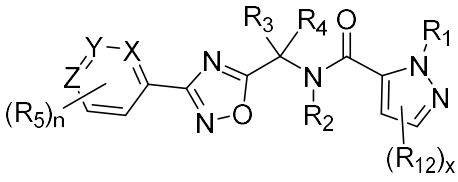
a compound of Formula **I-c**:


(**I-c**),

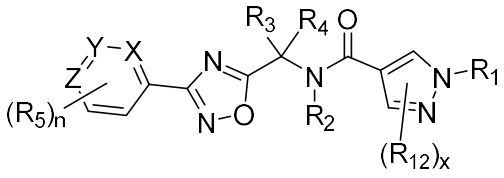
a compound of Formula **I-d**:


(**I-d**),

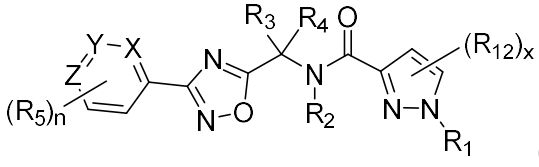
a compound of Formula **I-e**:


(**I-e**),

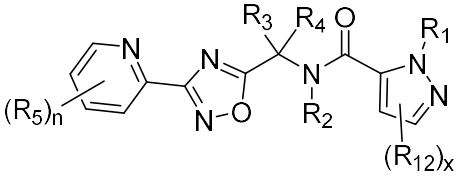
a compound of Formula **I-f**:


(**I-f**),

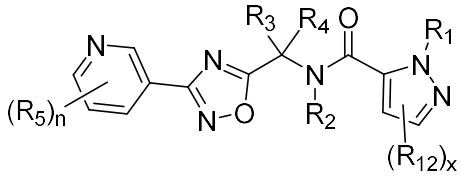
a compound of Formula **I-g**:


(**I-g**),

a compound of Formula **I-h**:

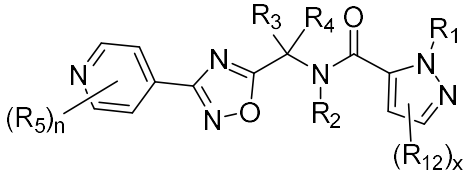

(**I-h**),

a compound of Formula **I-i**:



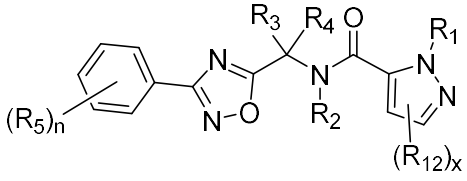
(**I-i**),

a compound of Formula **I-j**:



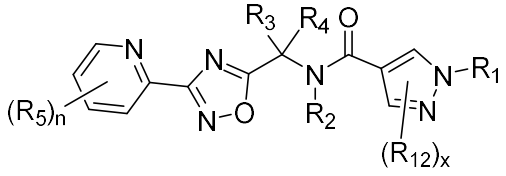
(**I-j**),

a compound of Formula **I-k**:



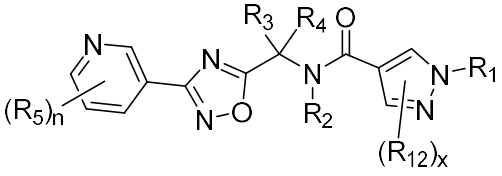
(**I-k**),

a compound of Formula **I-l**:



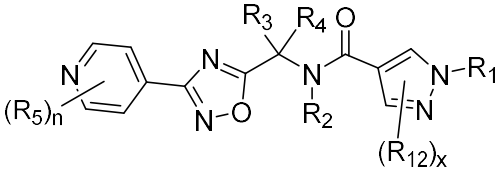
(**I-l**),

a compound of Formula **I-m**:



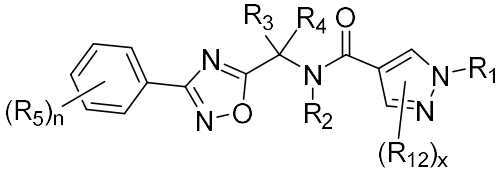
(**I-m**),

a compound of Formula **I-n**:



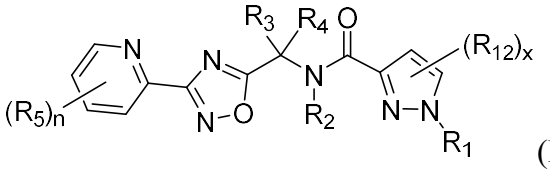
(**I-n**),

a compound of Formula **I-o**:



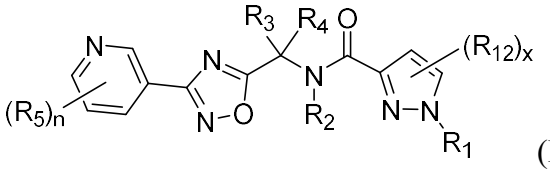
(**I-o**),

a compound of Formula **I-p**:



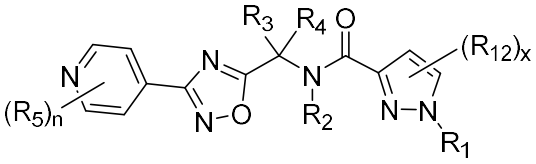
(**I-p**),

a compound of Formula **I-q**:



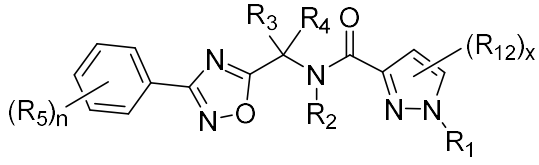
(**I-q**),

a compound of Formula **I-r**:



(**I-r**), or

a compound of Formula **I-s**:



(**I-s**),

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in claim 1.

4. The pharmaceutical composition of any one of claims 1-3, wherein R_2 is hydrogen or methyl.

5. The pharmaceutical composition of any one of claims 1-4, wherein R_3 is hydrogen, C_{1-6}alkyl, or C_{1-6}alkyl substituted with C_{1-6}alkoxy, -OH, or -C(O)OR_8.

6. The pharmaceutical composition of any one of claims 1-5, wherein R_4 is hydrogen.

7. The pharmaceutical composition of any one of claims 1-4, wherein R_3 and R_4 are taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene.

8. The pharmaceutical composition of claim 7, wherein the C_{3-7}cycloalkylene is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

9. The pharmaceutical composition of claim 7, wherein the 3-7 membered heterocyclene is selected from the group consisting of oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl.

10. The pharmaceutical composition of any one of claims 1-9, wherein each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-}

$_{6}$alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, O-C_{3-10}cycloalkyl, -OH, -CN, $N(R_9)_2$, and -$C(O)OR_8$.

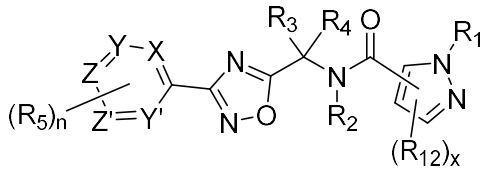
11. The pharmaceutical composition of any one of claims 1-10, wherein n is 1.

12. The pharmaceutical composition of any one of claims 1-11, wherein R_1 is selected from the group consisting of C_{1-6}alkyl optionally substituted with C_{1-6}alkoxy, $N(R_9)_2$, $C(O)N(R_9)_2$, C_{3-7}cycloalkyl, pyridyl, tetrahydropyranyl, or phenyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, phenyl optionally substituted with halogen, and pyridyl optionally substituted with halogen.

13. The pharmaceutical composition of any one of claims 1-12, wherein R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, and phenyl optionally substituted with halogen.

14. The pharmaceutical composition of any one of claims 1-13, wherein x is 1 or 2.

15. A compound of Formula **II**:



(**II**),

or a pharmaceutically acceptable salt thereof, wherein

one or two selected from X, Y, Z, Y', and Z' are N, and the others are CH, wherein the hydrogen of CH may be substituted with R_5;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy optionally substituted with C_{3-7}cycloalkyl, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, -$N(R_9)_2$, -C(O)OR_8, -C(O)$N(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)$N(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

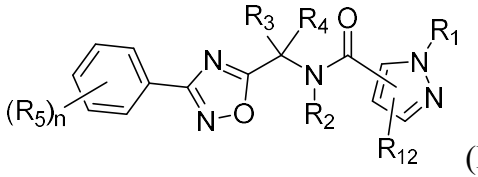
R_8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, and C_{3-10}cycloalkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl; and

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl.

16. A compound of Formula **III**:


(**III**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl is optionally substituted with one or more halogen or C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, and phenyl, wherein the C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, or phenyl is optionally substituted with one or more substituents each independently selected from halogen and C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -C(O)OR_8, -C(O)N(R_9)$_2$, -C_{1-6}alkylene-CN, -CN, -S(O)$_2$-C_{1-6}alkyl, C_{1-6}alkylene-S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$- N(R_9)$_2$, -OC(O)C_{1-6}alkyl, and -O-C_{1-3}cycloalkyl optionally substituted with one or more halogen;

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)N(R_9)$_2$,-NR_{10}C(O)-R_{11}, -CN, -S(O)$_2$-C_{1-6}alkyl, -S(O)$_2$- N(R_9)$_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -N(R_9)$_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached

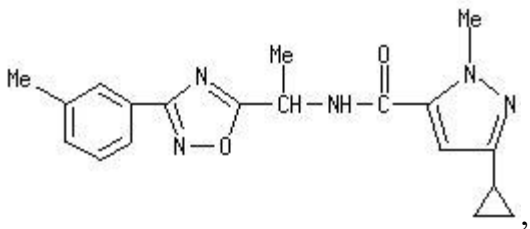
to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

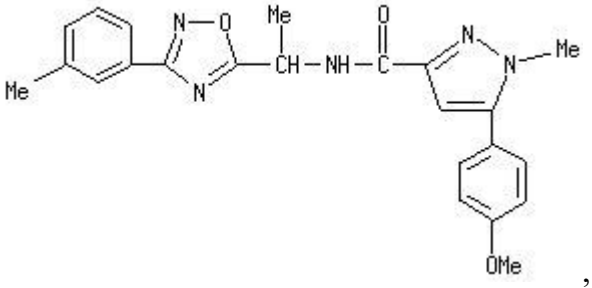
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

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

wherein the compound is not:

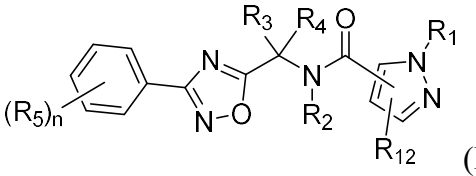


,



, or a pharmaceutically acceptable salt thereof.

17. A compound of Formula **IV**:



(**IV**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of C_{1-6}alkyl, and C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6}alkoxy;

R_{12} is C_{1-6}alkyl optionally substituted with one or more halogen or C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -C(O)OR_8, -C(O)$N(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-

$_6$alkylene-S(O)$_2$-C$_{1-6}$alkyl, -S(O)$_2$- N(R$_9$)$_2$, -OC(O)C$_{1-6}$alkyl, and -O-C$_{3-10}$cycloalkyl optionally substituted with one or more halogen;

R_7 is each independently selected from the group consisting of phenyl, C$_{1-6}$alkoxy, -OH, -O-(C$_{1-6}$alkylene)-phenyl, C$_{3-10}$cycloalkyl, -C(O)OR$_8$, -C(O)N(R$_9$)$_2$,-NR$_{10}$C(O)-R$_{11}$, -CN, -S(O)$_2$-C$_{1-6}$alkyl, -S(O)$_2$- N(R$_9$)$_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C$_{3-10}$cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C$_{1-6}$alkyl, halogen, -OH, C$_{1-6}$alkoxy, and -N(R$_9$)$_2$;

R_8 is hydrogen or C$_{1-6}$alkyl;

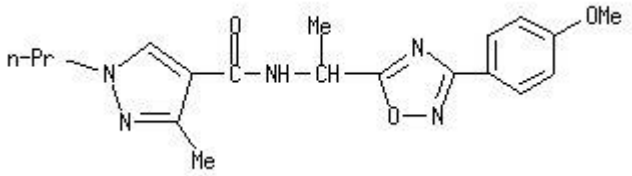
each R_9 is independently selected from the group consisting of hydrogen, C$_{1-6}$alkyl, and -(C$_{1-6}$alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents selected from halogen and -OH;

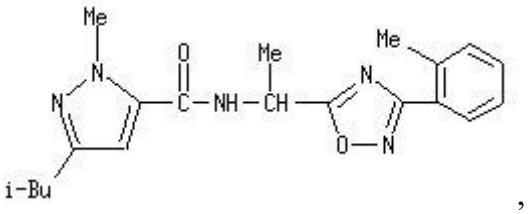
each R_{10} is independently hydrogen or C$_{1-6}$alkyl;

R_{11} is selected from the group consisting of C$_{1-6}$alkyl, C$_{1-6}$alkoxy, and -O-(C$_{1-6}$alkylene)-phenyl; and

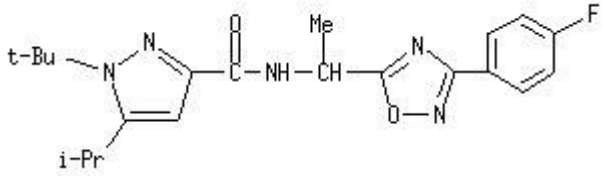
n is selected from the group consisting of 0, 1, 2, and 3;

wherein the compound is not:



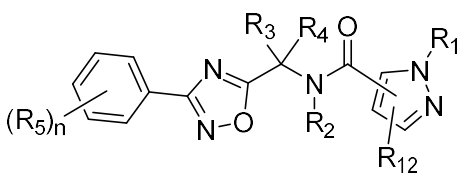
,


,



, or a pharmaceutically acceptable salt thereof.

18. A compound of Formula **V**:



(**V**),

or a pharmaceutically acceptable salt thereof, wherein

R_1 is phenyl or 3-10 membered heteroaryl, wherein the phenyl or 3-10 membered heteroaryl is optionally substituted with one or more substituents independently selected from halogen and C_{1-6}alkoxy,

R_{12} is selected from the group consisting of C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from halogen and C_{1-6}alkoxy;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

R_5 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, -C_{1-6}alkylene-OH, OH, -C(O)OR_8, -C(O)N$(R_9)_2$, -C_{1-6}alkylene-CN, -CN, -S$(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-S$(O)_2$-C_{1-6}alkyl, -S$(O)_2$- N$(R_9)_2$, -OC(O)C_{1-6}alkyl, and -O-C_{3-10}cycloalkyl;

R_7 is selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -O-(C_{1-6}alkylene)-phenyl, C_{3-7}cycloalkyl, -C(O)OR_8, -C(O)N$(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -S$(O)_z$-C_{1-6}alkyl, -S$(O)_z$- N$(R_9)_2$, 3-7 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -N$(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

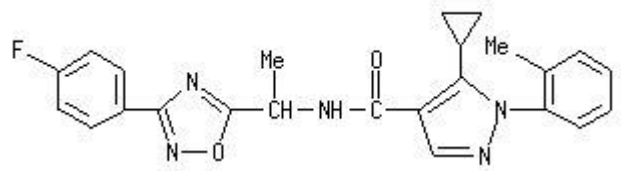
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

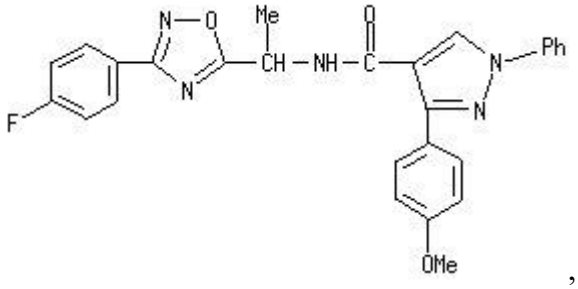
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

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

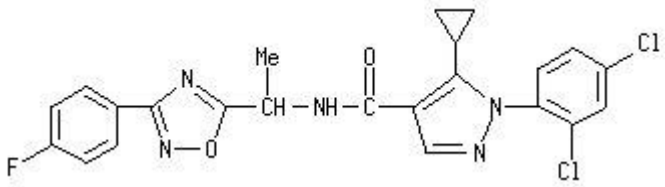
wherein the compound is not:



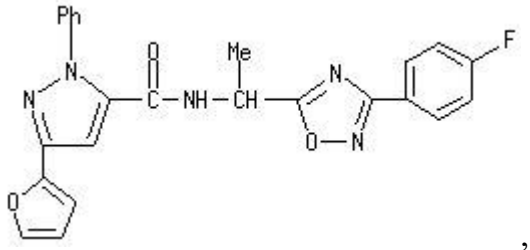
,



,



,

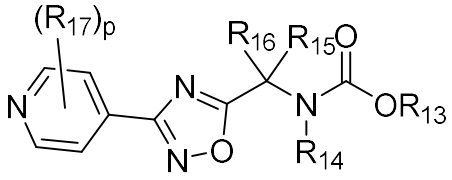


, or a pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of any one of claims 1-14 or the compound of any one of claims 15-18, wherein the compound is selected from the group consisting of Compound Nos. 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237 238, 239, 240, 241, 242, 243, 244, 245, 246, 248, 249, 250, 251,

252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 263, 264, 265, 266, 267, 268, 269, 270, 271, 278, 279, 280, 297, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, and 310 in the Examples, or a pharmaceutically acceptable salt thereof.

20. A compound of Formula **VI**:



(**VI**),

or a pharmaceutically acceptable salt thereof, wherein

R_{13} is $C_{1\text{-}6}$alkyl or $C_{3\text{-}10}$cycloalkyl, wherein the $C_{1\text{-}6}$alkyl or $C_{3\text{-}10}$cycloalkyl is optionally substituted with phenyl;

R_{14} is hydrogen;

R_{15} is $C_{1\text{-}6}$alkyl or hydrogen;

R_{16} is $C_{1\text{-}6}$alkyl optionally substituted with one or more halogen, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$ cycloalkyl, or phenyl;

each R_{17} is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkylene-$N(R_{20})_2$, $C_{1\text{-}6}$alkylene-O-$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy optionally substituted with $C_{3\text{-}7}$cycloalkyl, $C_{1\text{-}6}$haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or $C_{1\text{-}6}$alkoxy, 3-10 membered heteroaryl, -$C_{1\text{-}6}$alkylene-OH, $C_{1\text{-}6}$alkylene-$C_{1\text{-}6}$alkoxy, OH, -$N(R_{20})_2$, -$C(O)OR_{19}$, -$C(O)N(R_{20})_2$, -$C_{1\text{-}6}$alkylene-CN, -CN, -$S(O)_2$-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylene-$S(O)_2$-$C_{1\text{-}6}$alkyl, -$S(O)_2$- $N(R_{20})_2$, -$OC(O)C_{1\text{-}6}$alkyl, -O-$C_{3\text{-}10}$cycloalkyl optionally substituted with one or more halogen or $C_{1\text{-}6}$alkyl, and $C_{3\text{-}10}$cycloalkyl optionally substituted with one or more substituents selected from halogen, $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkoxy;

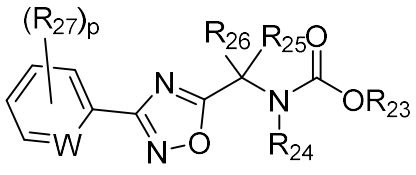
p is selected from the group consisting of 1, 2, and 3;

R_{19} is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, and $C_{3\text{-}10}$cycloalkyl;

each R_{20} is independently hydrogen or $C_{1\text{-}6}$alkyl; and

each R_{21} is independently hydrogen or $C_{1\text{-}6}$alkyl.

21. A pharmaceutical composition comprising a compound of Formula **VII**:



(**VII**),

or a pharmaceutical acceptable salt thereof, wherein

W is N or CH;

R_{23} is C_{1-6}alkyl;

R_{24} is hydrogen;

R_{25} is C_{1-6}alkyl or hydrogen;

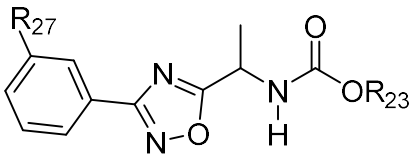
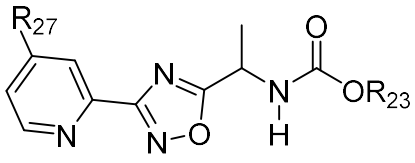
R_{26} is C_{1-6}alkyl optionally substituted with one or more halogen or C_{1-6}alkoxy;

each R_{27} is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; and

p is selected from the group consisting of 1, 2, and 3;

and a pharmaceutically acceptable excipient.

22. The pharmaceutical composition of claim 21, wherein the compound is a compound of Formula **VII-a** or Formula **VII-b**:

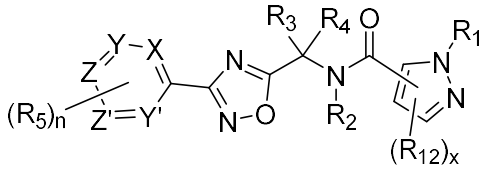

(**VII-a**),

(**VII-b**),

or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition of claim 21, wherein the compound is selected from the group consisting of Compound Nos. 281, 282, 283, and 285 in the Examples, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any one of claims 15-20 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

25. Use of a compound of Formula **I**:


(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a neurological disease or disorder, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with

one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, $-C(O)OR_8$, $C(O)N(R_9)_2$, C_{1-6}alkylene-CN, -CN, $-S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, $-S(O)_2$-$N(R_9)_2$, $-OC(O)C_{1-6}$alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, $-N(R_9)_2$, $-NR_9$-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, $-C(O)OR_8$, $-C(O)N(R_9)_2$,$-NR_{10}C(O)$-R_{11}, -CN, $-S(O)_2$-C_{1-6}alkyl, $-S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or

more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -N(R_9)$_2$;

R_8 is hydrogen or C_{1-6}alkyl;

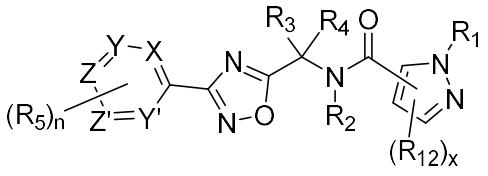
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

26. Use of a compound of Formula **I**:



(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with excessive neuronal excitability, wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, C(O)N(R_9)$_2$, N(R_9)$_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, -C(O)OR_8, C(O)$N(R_9)_2$, C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, -$N(R_9)_2$, -NR_9-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)$N(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and -$N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

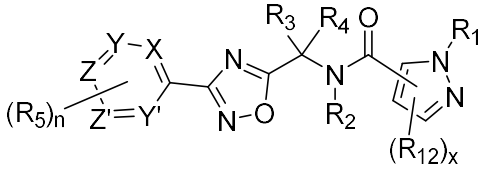
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

27. Use of a compound of Formula **I**:



(**I**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with a gain-of-function mutation of a gene (e.g., KCNT1), wherein

X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be substituted with R_5, wherein at least 3 selected from X, Y, Z, Y', and Z' are CH;

R_1 is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, $C(O)N(R_9)_2$, $N(R_9)_2$, C_{3-7}cycloalkyl, phenyl, 3-10 membered heteroaryl, and C_{1-6}alkoxy;

R_{12} is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, or phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halogen, -OH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; or

two R_{12} on adjacent carbons can be taken together with the two carbons where R_{12} are attached to form a carbocyclic ring;

x is 0, 1 or 2;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, and phenyl; and R_4 is selected from C_{1-6}alkyl and hydrogen; or R_3 and R_4 can be taken together with the carbon attached to R_3 and R_4 to form a C_{3-7}cycloalkylene or 3-7 membered heterocyclene; wherein the C_{1-6}alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, 3-10 membered heteroaryl, phenyl, C_{3-7}cycloalkylene, or 3-7 membered heterocyclene may be optionally substituted with one or more R_7;

each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted with C_{3-10}cycloalkyl optionally substituted with one or more halogens, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted with one or more halogens or C_{1-6}alkoxy, 3-10 membered heteroaryl, C_{1-6}alkylene-OH, C_{1-6}alkylene-C_{1-6}alkoxy, OH, $N(R_9)_2$, -C(O)OR_8, C(O)$N(R_9)_2$, C_{1-6}alkylene-CN, -CN, -$S(O)_2$-C_{1-6}alkyl, C_{1-6}alkylene-$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$-$N(R_9)_2$, -OC(O)C_{1-6}alkyl, -O-C_{3-10}cycloalkyl optionally substituted with one or more halogen or C_{1-6}alkyl, and C_{3-10}cycloalkyl optionally substituted with one or more substituents selected from halogen, C_{1-6}alkyl, and C_{1-6}alkoxy;

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

R_7 is each independently selected from the group consisting of phenyl, C_{1-6}alkoxy, -OH, $-N(R_9)_2$, $-NR_9$-SO_2-C_{1-6}alkyl, -O-(C_{1-6}alkylene)-phenyl, C_{3-10}cycloalkyl, -C(O)OR_8, -C(O)$N(R_9)_2$,-NR_{10}C(O)-R_{11}, -CN, -$S(O)_2$-C_{1-6}alkyl, -$S(O)_2$- $N(R_9)_2$, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein the phenyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, halogen, -OH, C_{1-6}alkoxy, and $-N(R_9)_2$;

R_8 is hydrogen or C_{1-6}alkyl;

each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

each R_{10} is independently hydrogen or C_{1-6}alkyl;

R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

when R_3 and R_4 are both hydrogen, at least one selected from X, Y, Z, Y', and Z' is N.

28. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-24, 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).

29. The use of any one of claims 25-28, 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.

30. The use of any one of claims 25-28, 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.

31. The use of any one of claims 25-28, 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.

32. The use of any one of claims 25-28, 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).

33. The use of any one of claims 25-28, 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.

34. The use of any one of claims 25-28, 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).

35. The use of any one of claims 25-28, 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).

36. The use of any one of claims 25-28, 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.

37. The use of any one of claims 25-28, 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).

38. The use of any one of claims 25-28, 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.

39. The use of any one of claims 25-28, 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.