X, Y, Z, Y', and Z' are each independently selected from CH and N, wherein the hydrogen of CH may be replaced 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;

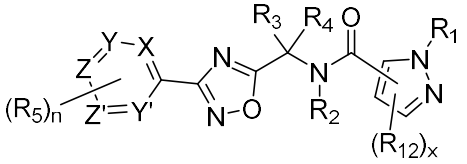
each R_{10} is independently hydrogen or C_{1-6}alkyl;

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.

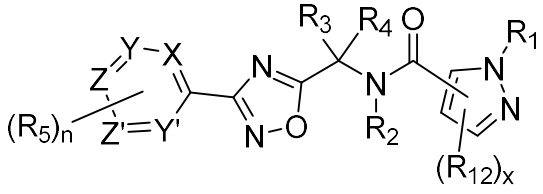
[0005] In another example, the present disclosure features a compound of Formula (II):



(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 replaced 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;

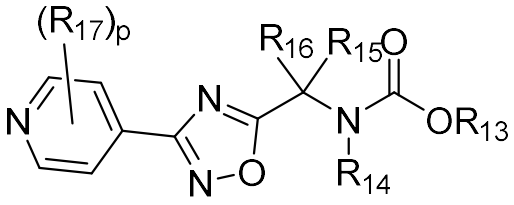
each R_5 is independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-$N(R_9)_2$, C_{1-6}alkylene-O-C_{3-10}cycloalkyl, C_{1-6}alkoxy optionally substituted with C_{3-7}cycloalkyl, C_{1-6}haloalkoxy, 3-10 membered heterocyclyl optionally substituted 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;

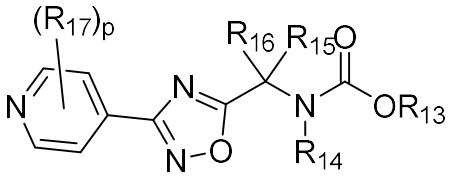
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to



(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;

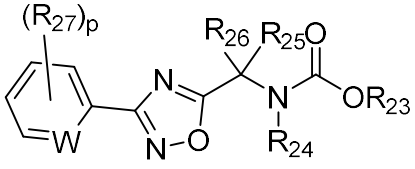
each R_{17} is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkylene-$N(R_{20})_2$, $C_{1\text{-}6}$alkylene-O-$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy optionally substituted with $C_{3\text{-}7}$cycloalkyl, $C_{1\text{-}6}$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; and

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

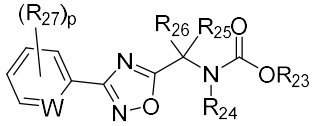
[00010] In another example, the present disclosure features a pharmaceutical composition comprising a compound of Formula (VII):



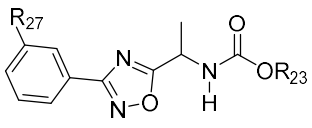
(VII),

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

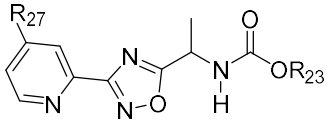
[00010a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula **VII**:



(**VII**), wherein the compound is a compound of Formula **VII-a** or Formula **VII-b**:



(**VII-a**),



(**VII-b**),

or a pharmaceutically acceptable salt thereof, wherein

R_{23} is a tert-butyl;

R_{24} is hydrogen;

R_{25} is hydrogen; and

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

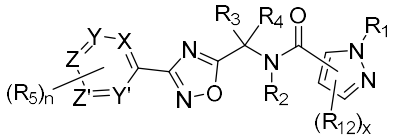
and a pharmaceutically acceptable excipient.

[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 replaced 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

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

[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).

[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.

[00015a] 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), 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.

[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.

[00016a] 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), 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.

[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.

[00017a] 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), 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.

[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).

[00018a] 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), 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).

[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.

[00019a] 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), 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 (SUDEP), 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).

[00020a] 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), 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).

[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).

[00021a] 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), 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.

[00022a] 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), 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.

[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).

[00023a] In one aspect, the present disclosure refers to use of a compound disclosed herein or a pharmaceutical composition of any one of 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), 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).

[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.

[00024a] 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), 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.

[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

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.

[00025a] 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), 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 (SUDEP), Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

[00026] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

DETAILED DESCRIPTION OF THE INVENTION

[00027] As generally described herein, the present invention provides compounds and compositions useful for preventing and/or treating a disease, disorder, or condition described herein, e.g., a disease, disorder, or condition associated with excessive neuronal excitability, and/or a disease, disorder, or condition associated with gain-of-function mutations in KCNT1. Exemplary diseases, disorders, or conditions include epilepsy and other encephalopathies (e.g., epilepsy of infancy with migrating focal seizures (MMFSI, EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), West syndrome, infantile spasms, epileptic encephalopathy, focal epilepsy, Ohtahara syndrome, developmental and epileptic encephalopathy, and Lennox Gastaut syndrome, seizures, leukodystrophy, leukoencephalopathy, intellectual disability, Multifocal Epilepsy, Generalized tonic clonic seizures, Drug resistant epilepsy, Temporal lobe epilepsy, cerebellar ataxia, Asymmetric Tonic Seizures) and cardiac dysfunctions (e.g., cardiac arrhythmia, Brugada syndrome, sudden unexpected death in epilepsy, myocardial infarction), pain and related conditions (e.g. neuropathic pain, acute/chronic pain, migraine, etc), muscle disorders (e.g. myotonia, neuromyotonia, cramp muscle spasms, spasticity), itch and pruritis, ataxia and cerebellar ataxias, psychiatric disorders (e.g. major depression, anxiety, bipolar disorder, schizophrenia), learning disorders, Fragile X, neuronal plasticity, and autism spectrum disorders.

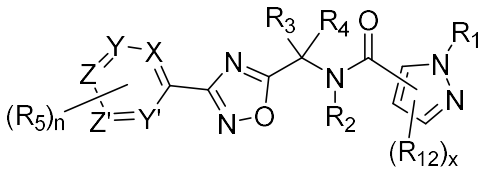
Definitions

Chemical Definitions

[00028] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic

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 replaced 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;

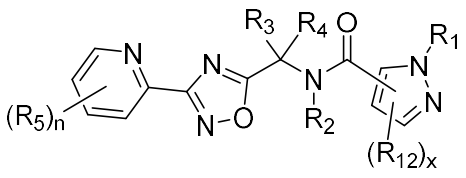
R_{11} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, and -O-(C_{1-6}alkylene)-phenyl; and

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.

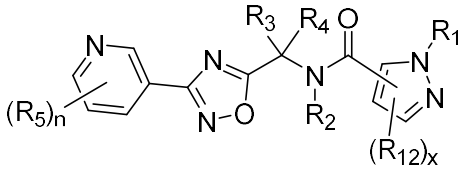
2. The pharmaceutical composition of claim 1, wherein one of X, Y, Z, Y', and Z' is N and the other four are CH.

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

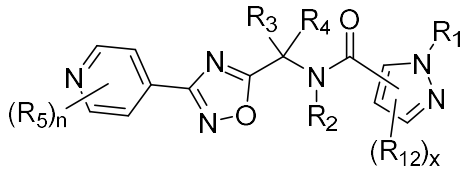


(**I-a**),

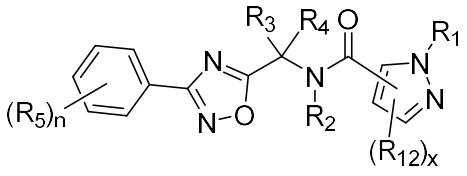
a compound of Formula **I-b**:


(**I-b**),

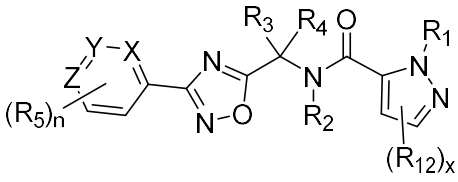
a compound of Formula **I-c**:


(**I-c**),

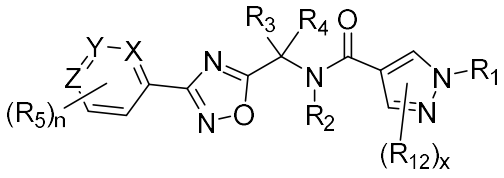
a compound of Formula **I-d**:


(**I-d**),

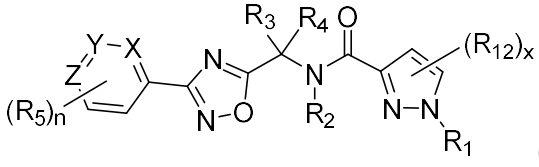
a compound of Formula **I-e**:


(**I-e**),

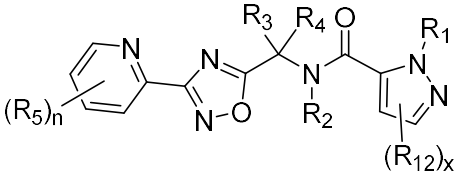
a compound of Formula **I-f**:


(**I-f**),

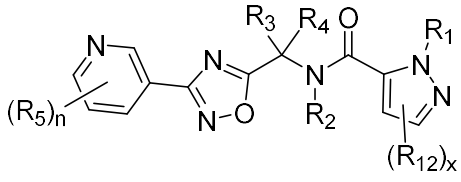
a compound of Formula **I-g**:


(**I-g**),

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

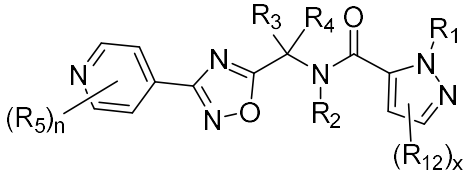

(**I-h**),

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



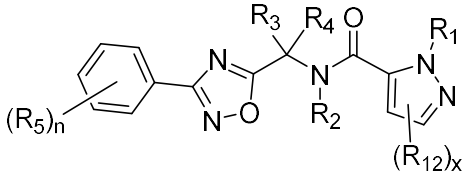
(**I-i**),

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



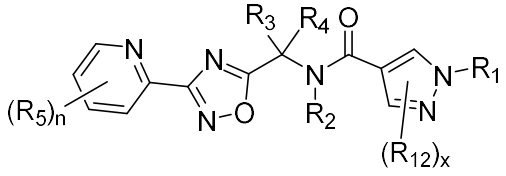
(**I-j**),

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



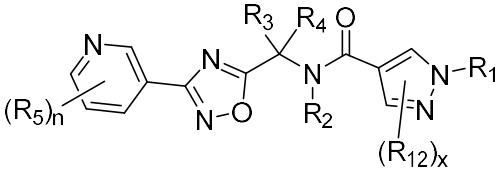
(**I-k**),

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



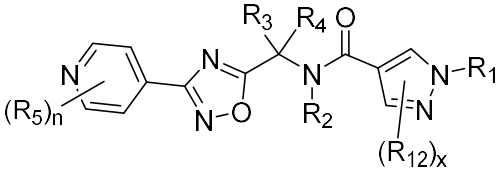
(**I-l**),

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



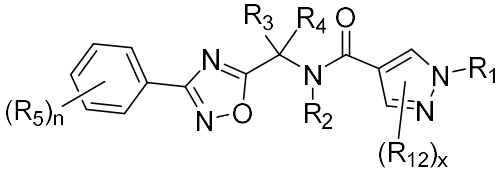
(**I-m**),

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



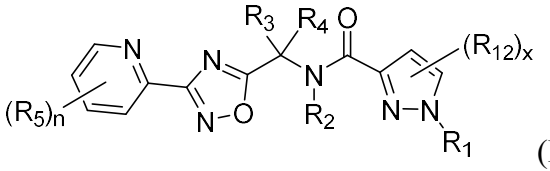
(**I-n**),

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



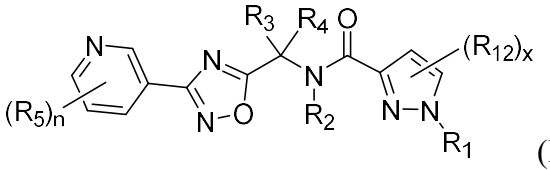
(**I-o**),

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



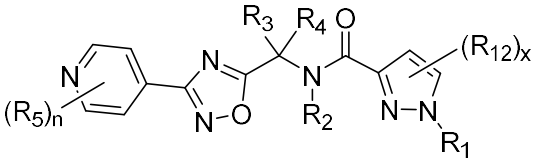
(**I-p**),

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



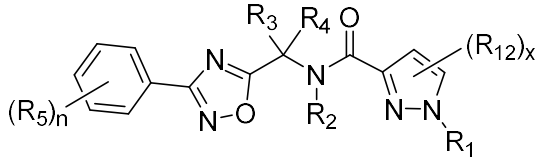
(**I-q**),

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 -$C(O)OR_8$.

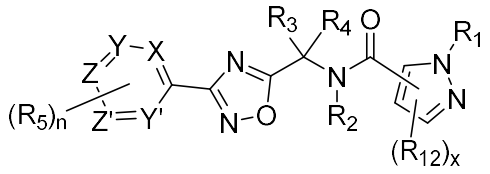
11. The pharmaceutical composition of any one of claims 1-10, wherein n is 1.

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 replaced 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 -$N(R_9)_2$;

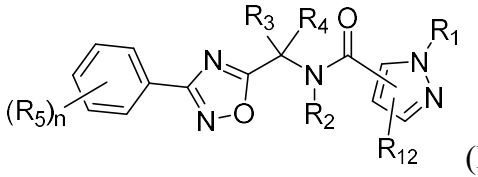
R_8 is selected from the group consisting of hydrogen, C_{1-6}alkyl, and C_{3-10}cycloalkyl;

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

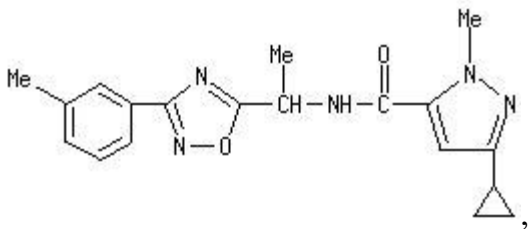
to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected from halogen and -OH;

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:



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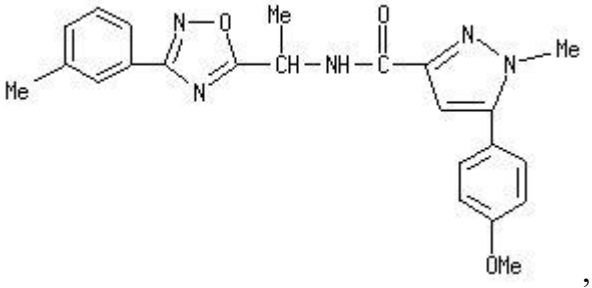
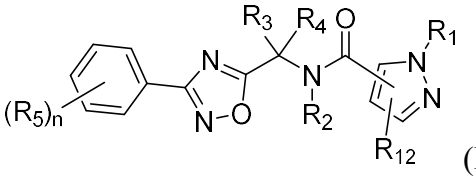


, or a pharmaceutically acceptable salt thereof.

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;

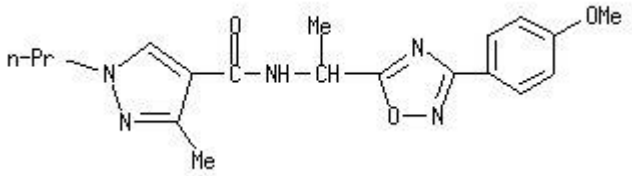
each R_9 is independently selected from the group consisting of hydrogen, C$_{1-6}$alkyl, and -(C$_{1-6}$alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents selected from halogen and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



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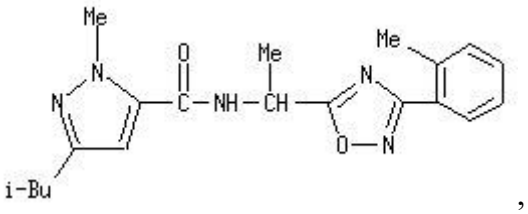

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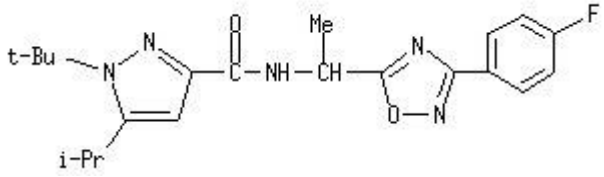
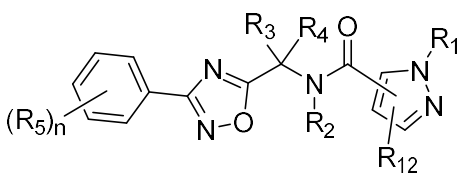


, or a pharmaceutically acceptable salt thereof.

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;

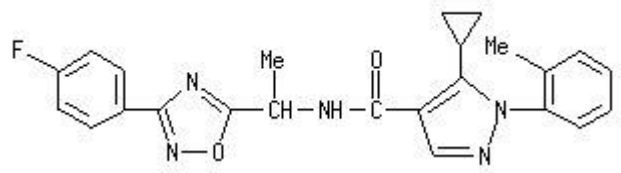
each R_9 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and -(C_{1-6}alkylene)-OH, or the two R_9 can be taken together with the nitrogen atom attached to the two R_9 to form a heterocycle optionally substituted with one or more substituents each independently selected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



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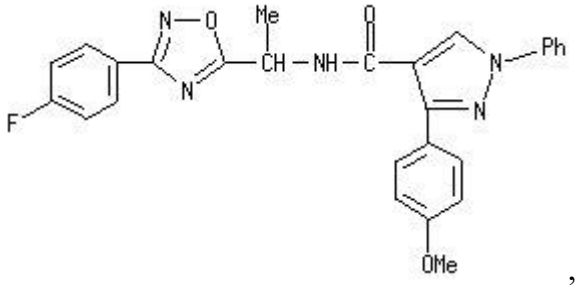

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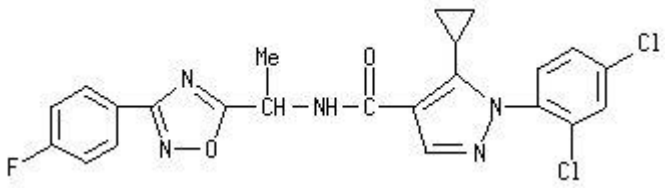

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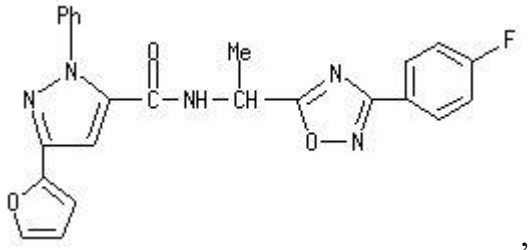
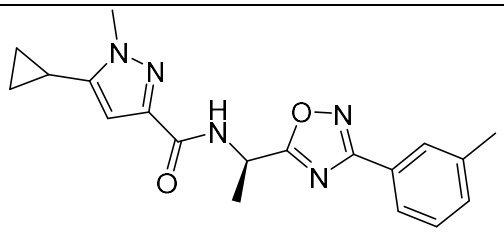
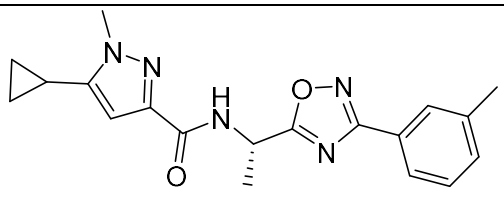
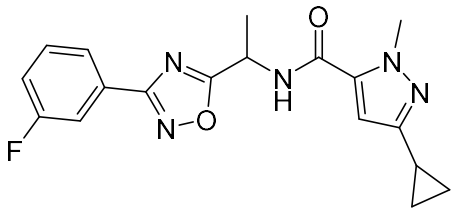
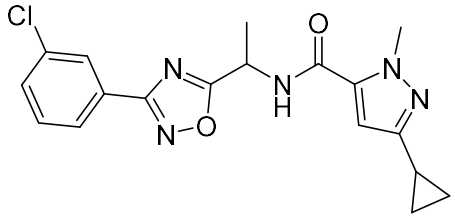
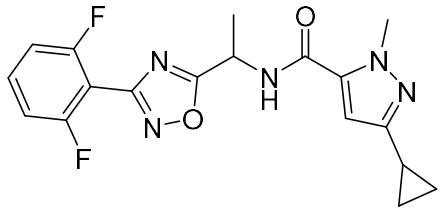
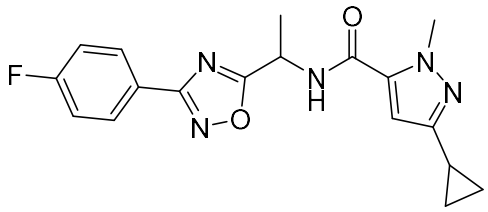
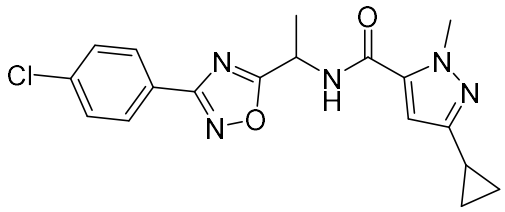
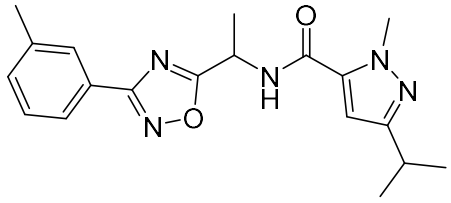
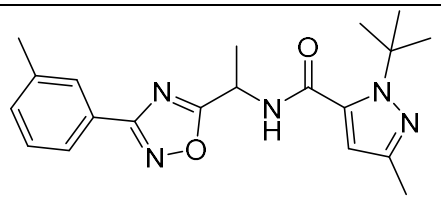
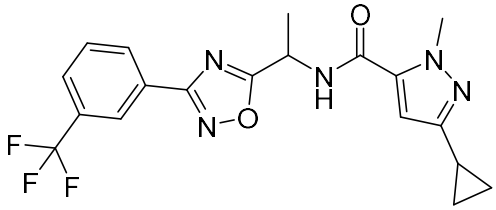
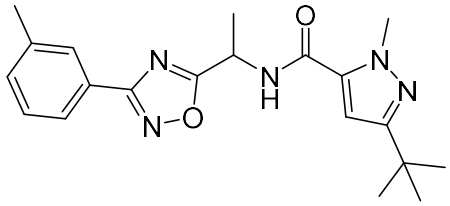
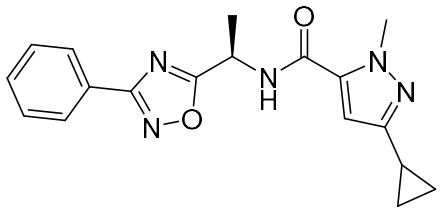
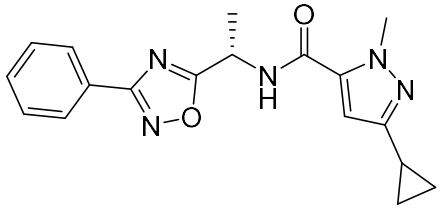
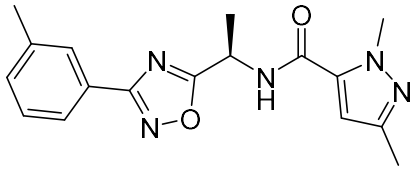
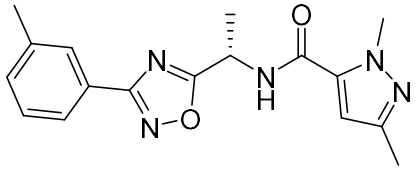
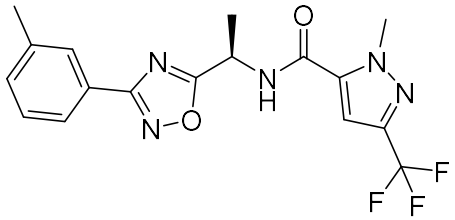


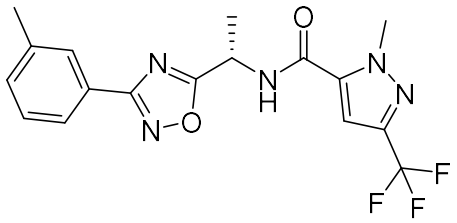
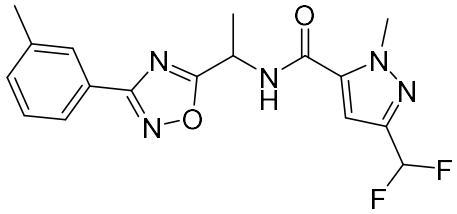
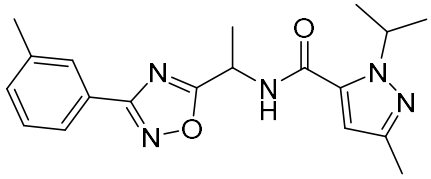
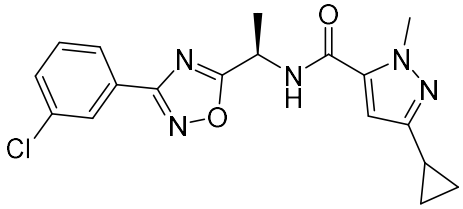
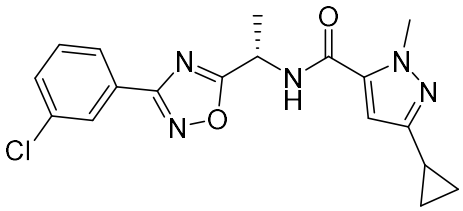
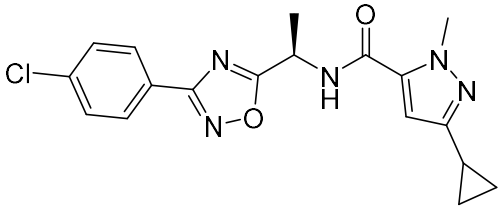
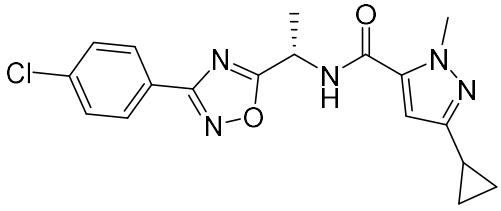
, or a pharmaceutically acceptable salt thereof.

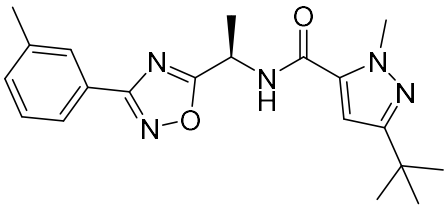
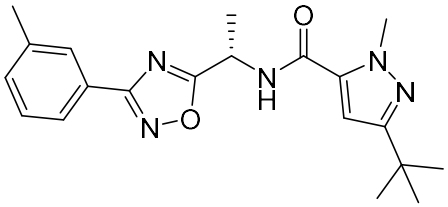
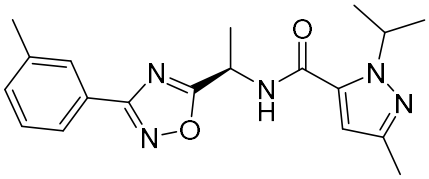
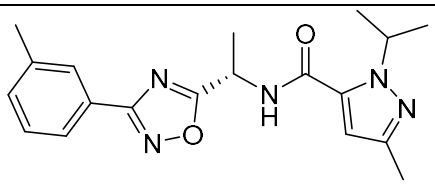
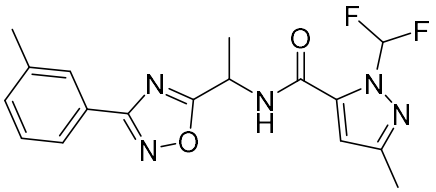
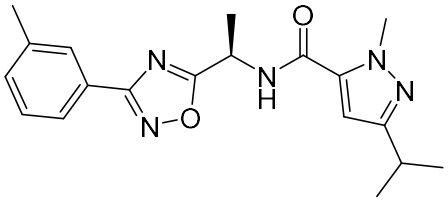
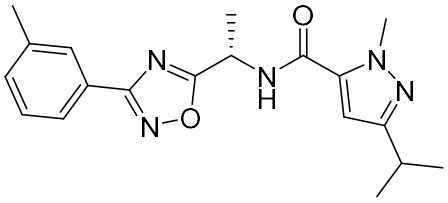
19. The pharmaceutical composition of any one of claims 1-14 or the compound of any one of claims 15-18, wherein the compound is selected from the group consisting of

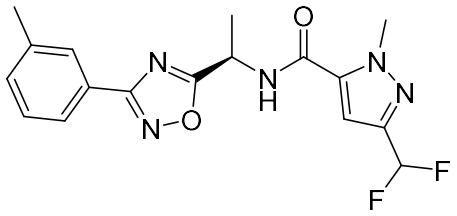
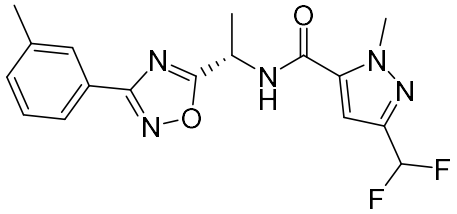
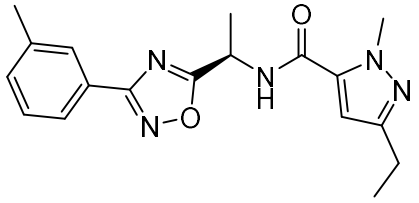
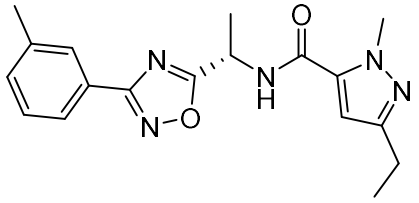
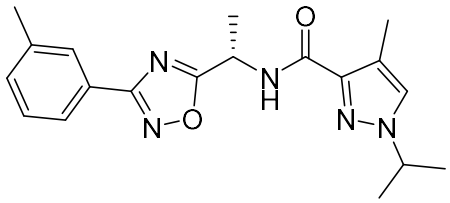
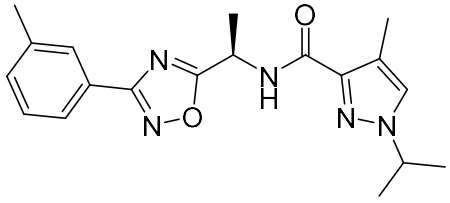
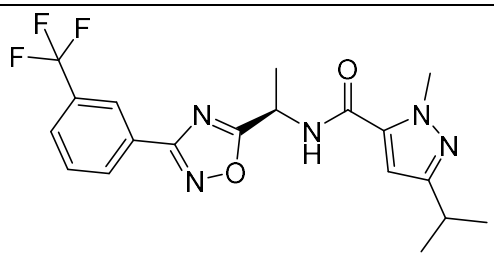
3	
4	

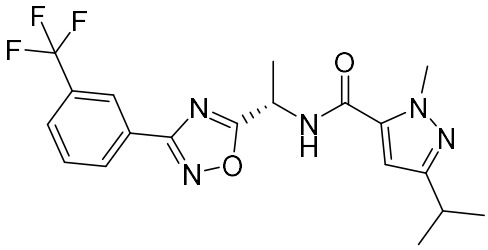
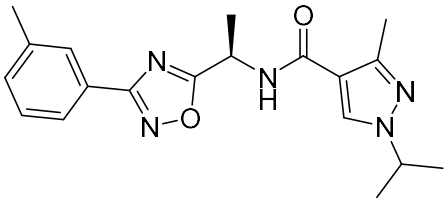
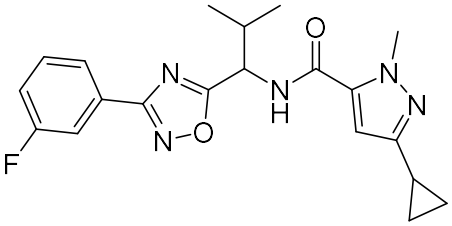
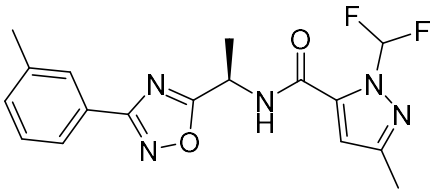
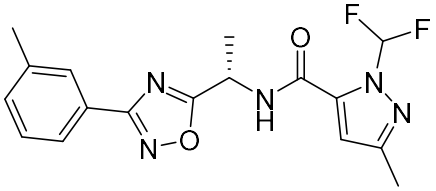
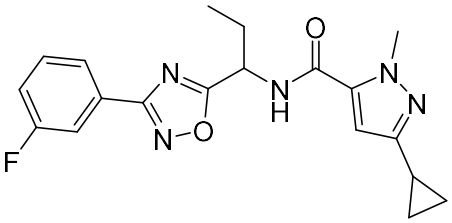
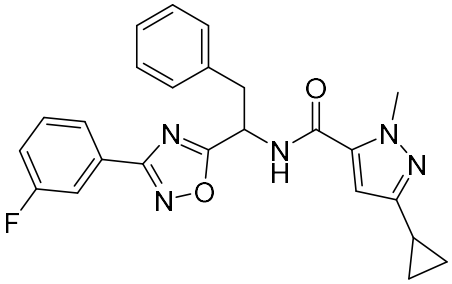
5	
6	
7	
8	
9	
10	
11	

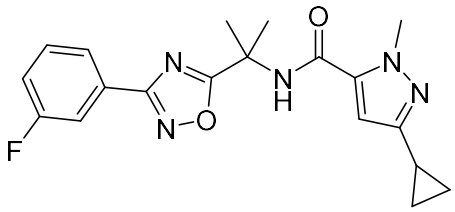
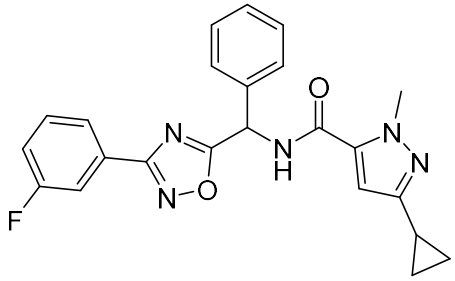
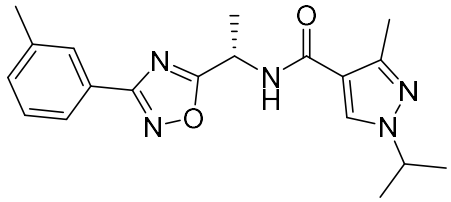
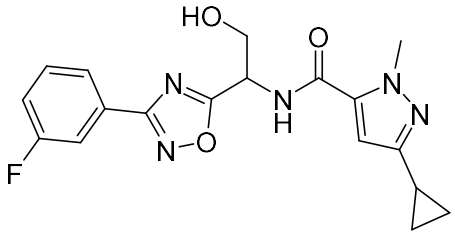
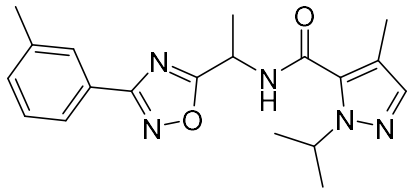
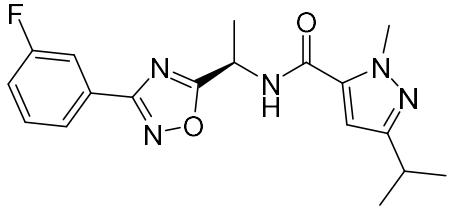
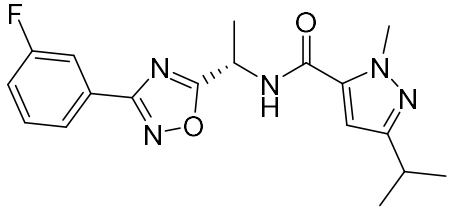
12	
13	
14	
15	
16	
17	
19	

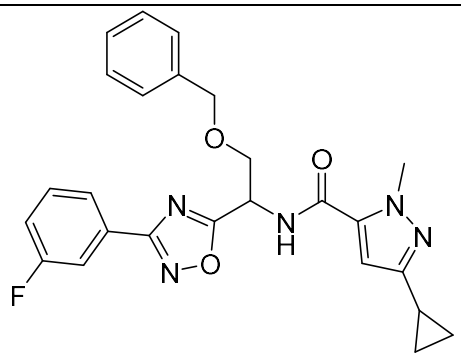
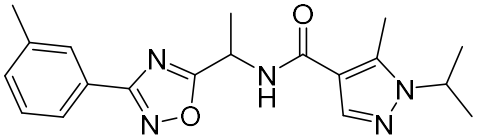
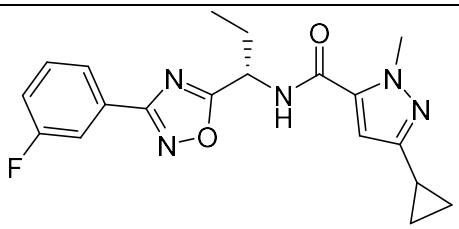
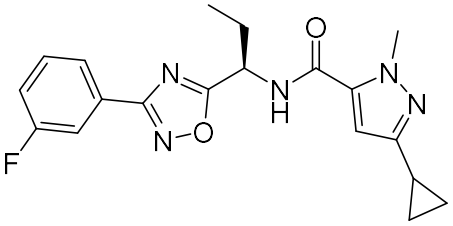
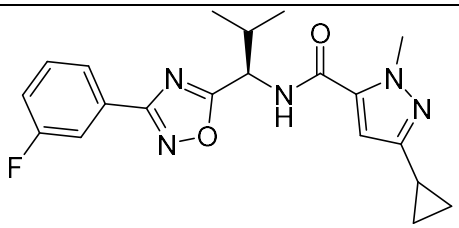
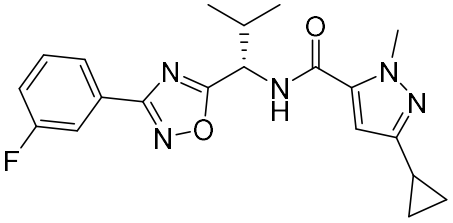
20	
21	
22	
23	
24	
25	
26	

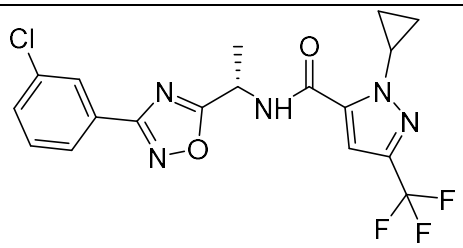
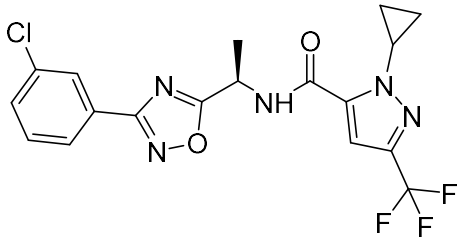
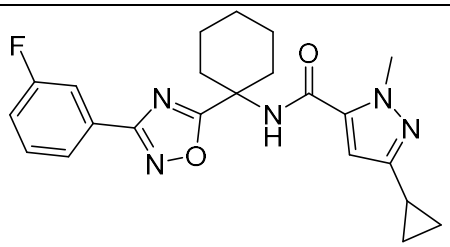
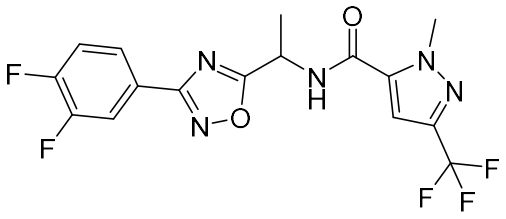
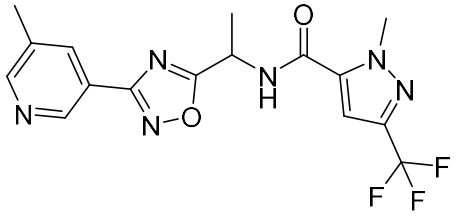
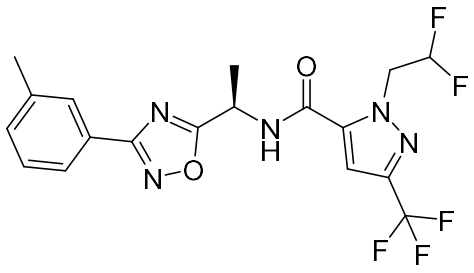
29	
30	
31	
32	
33	
34	
35	

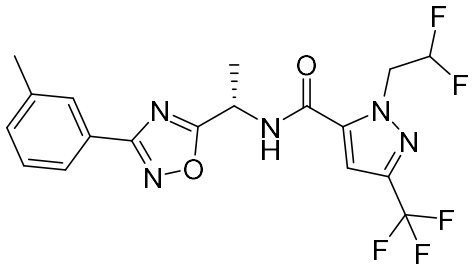
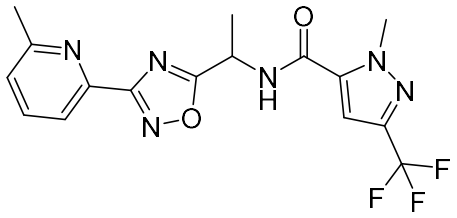
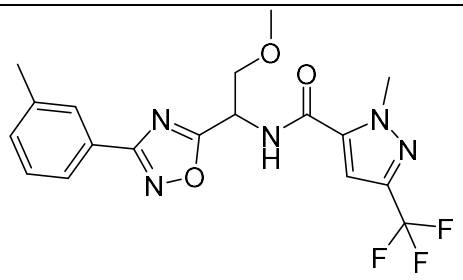
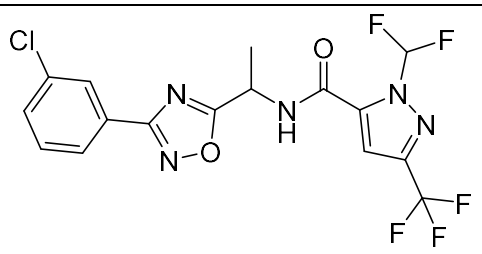
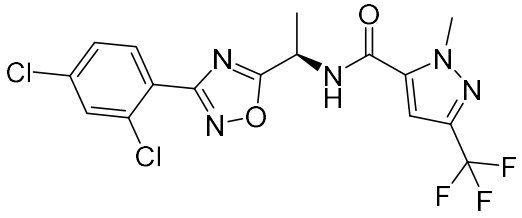
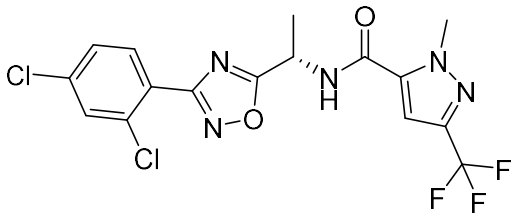
36	
37	
38	
39	
40	
41	
42	

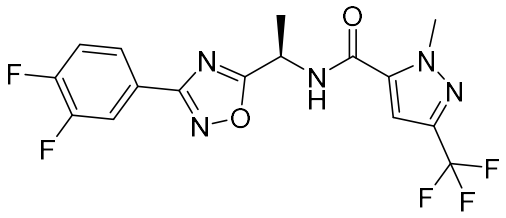
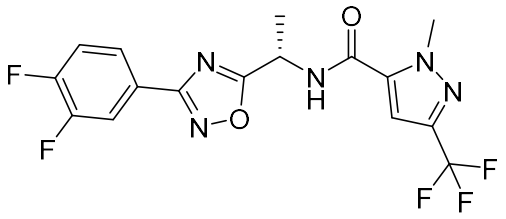
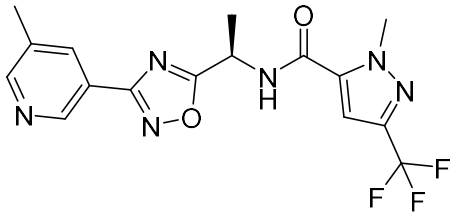
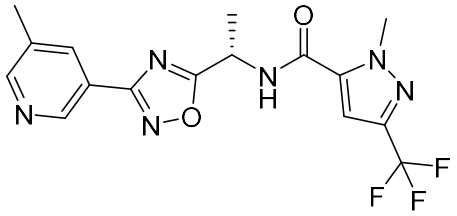
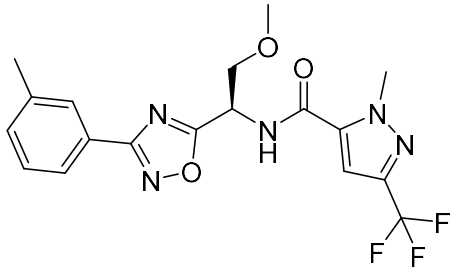
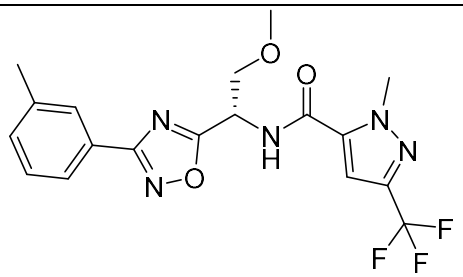
43	
44	
45	
46	
47	
48	
49	

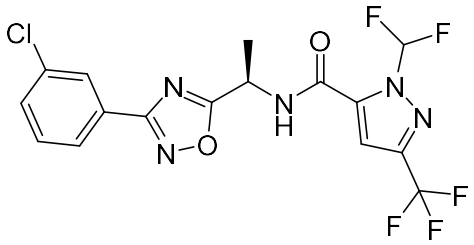
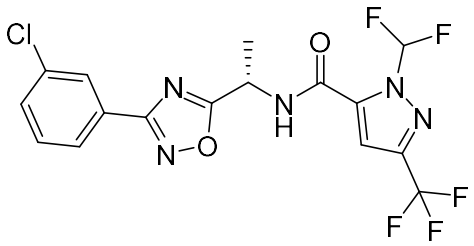
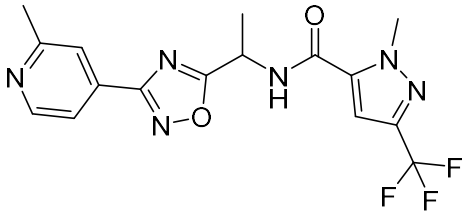
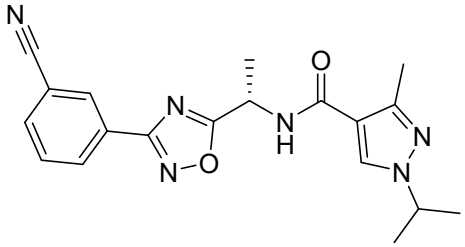
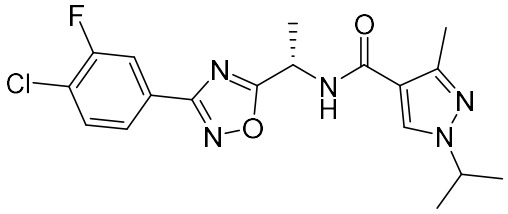
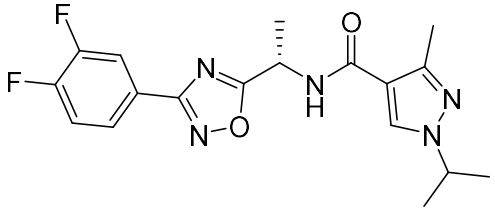
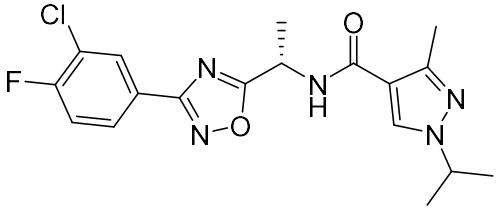
50	
51	
52	
54	
55	
56	
57	

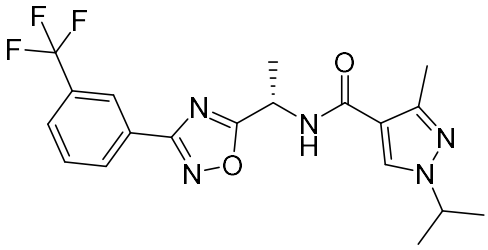
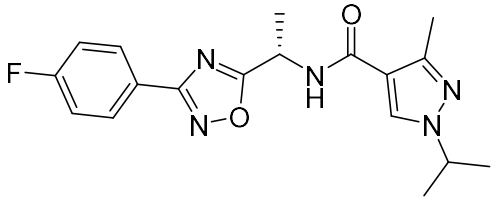
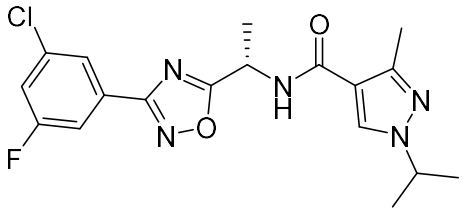
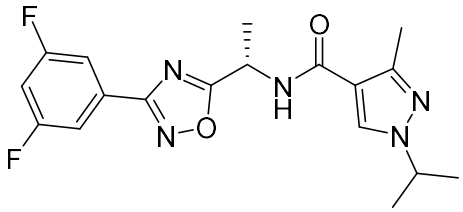
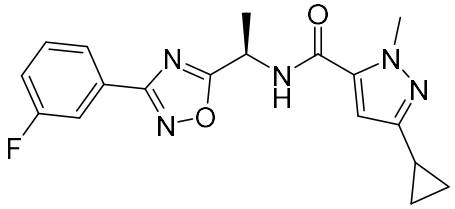
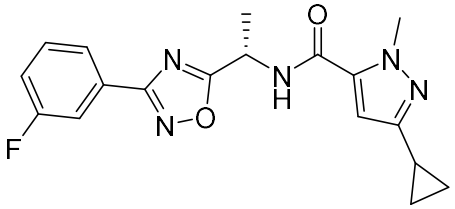
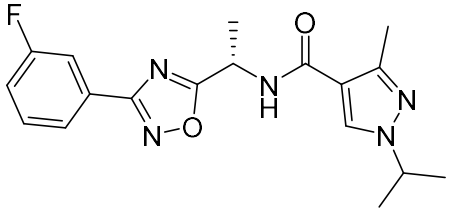
58	
59	
60	
61	
62	
63	

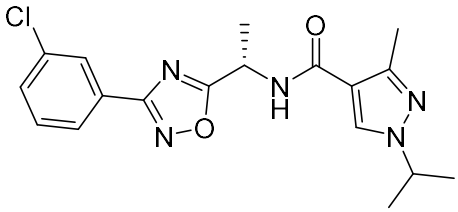
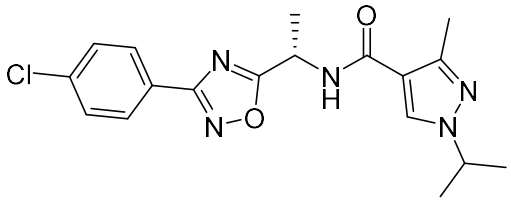
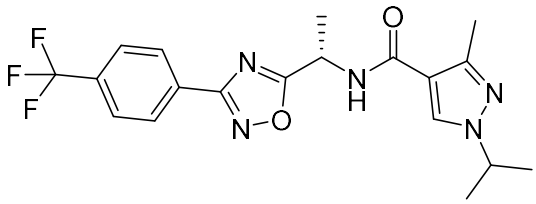
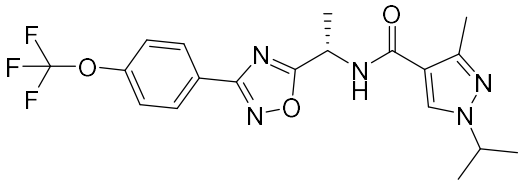
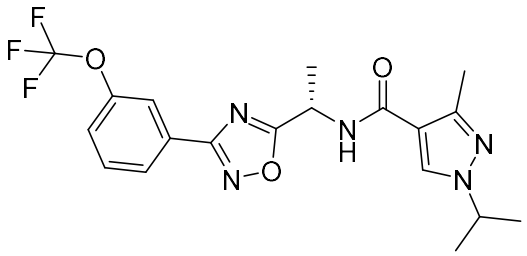
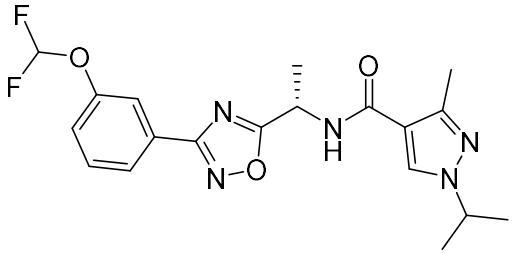
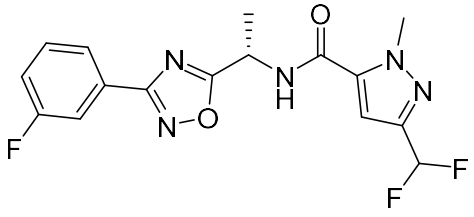
64	
65	
66	
67	
68	
69	

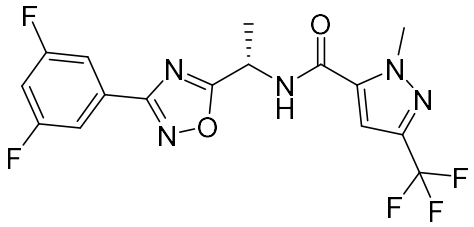
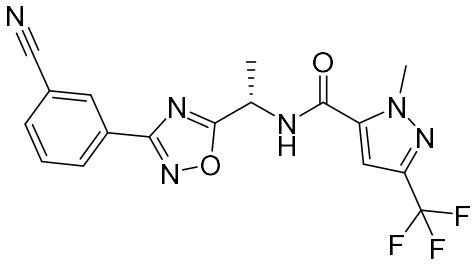
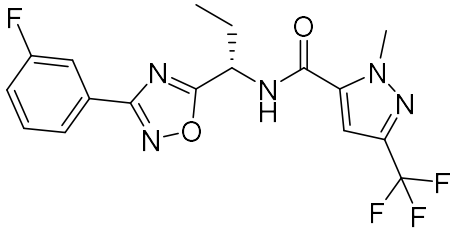
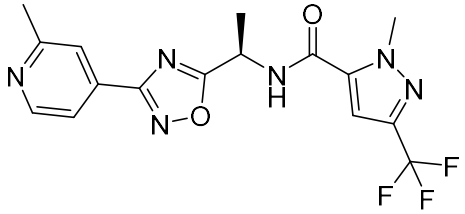
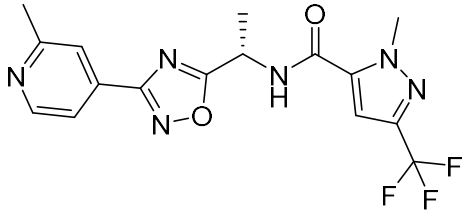
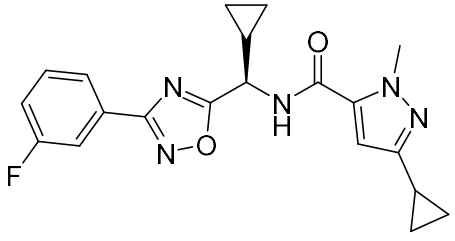
70	
71	
72	
73	
74	
75	

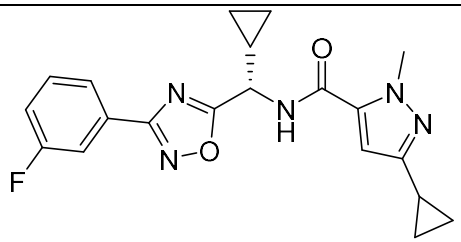
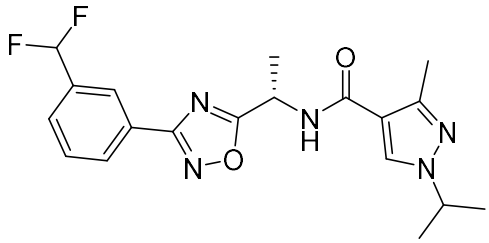
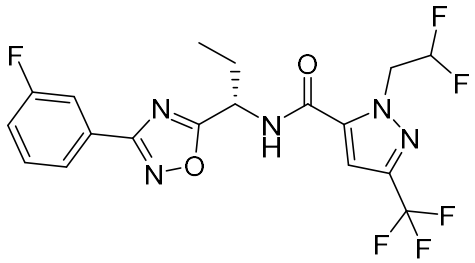
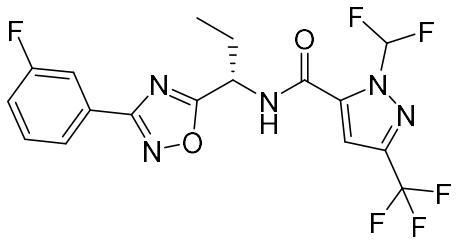
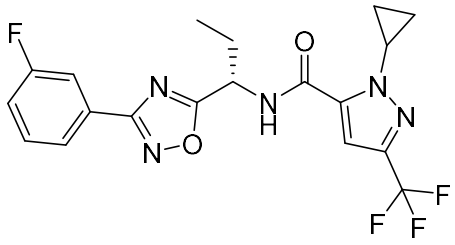
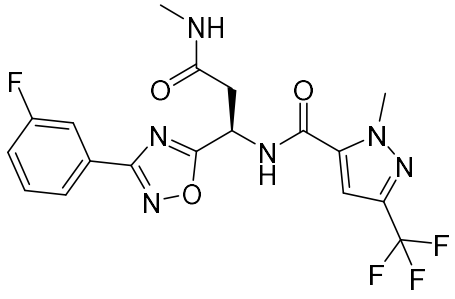
76	
77	
78	
79	
80	
81	

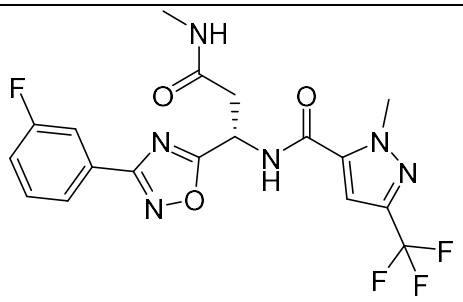
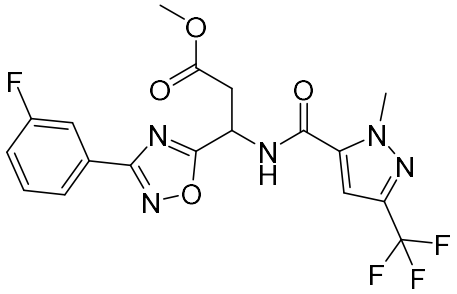
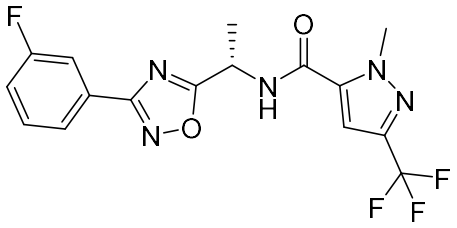
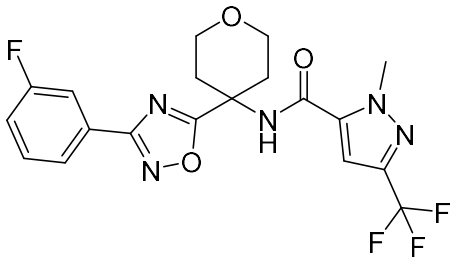
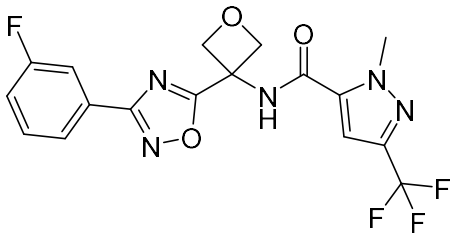
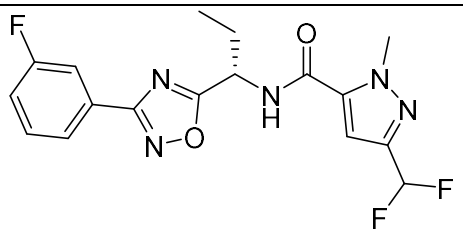
82	
83	
84	
85	
86	
87	
88	

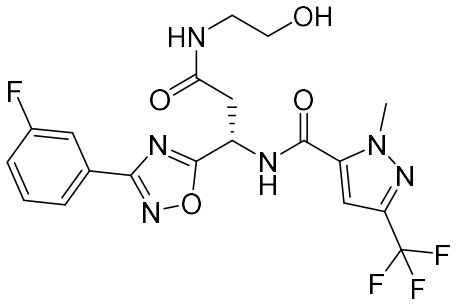
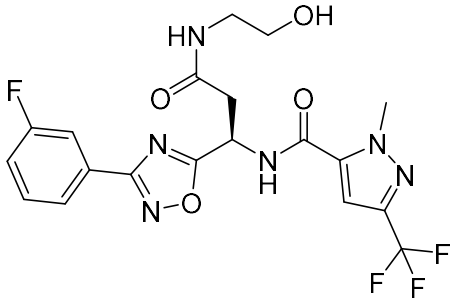
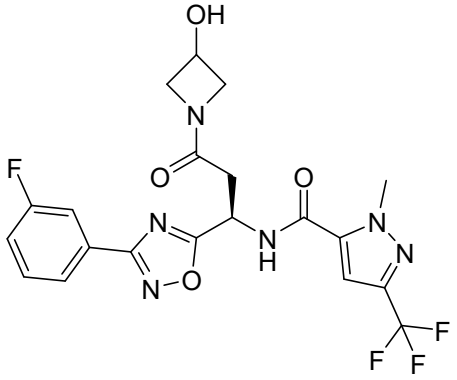
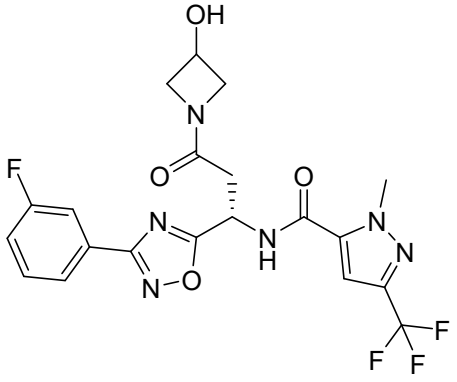
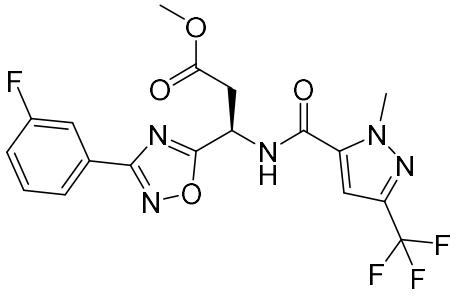
89	
90	
91	
92	
93	
94	
95	

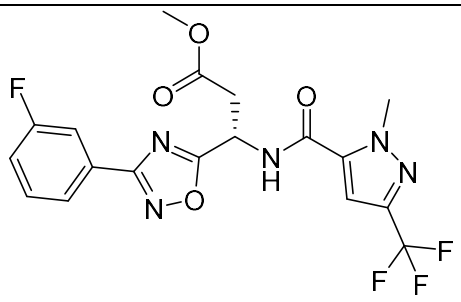
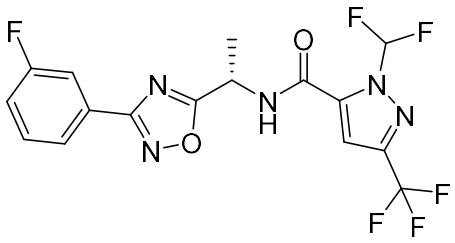
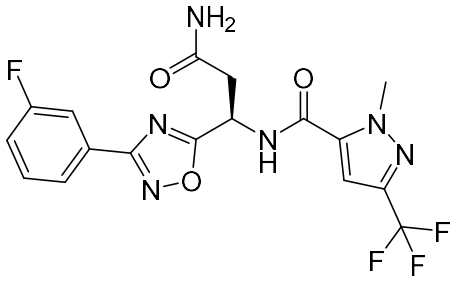
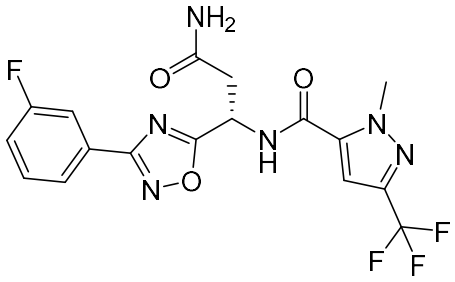
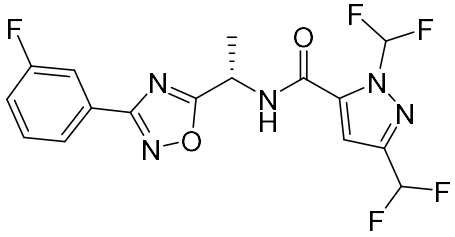
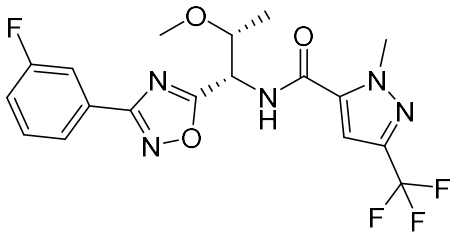
96	
97	
98	
99	
100	
101	
102	

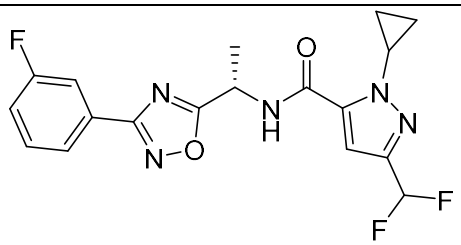
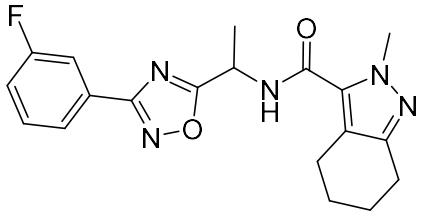
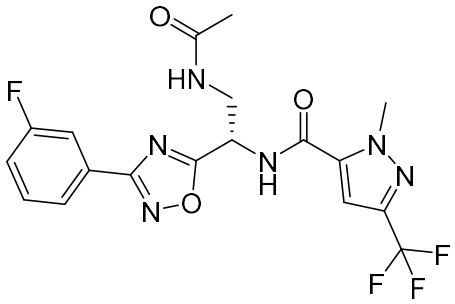
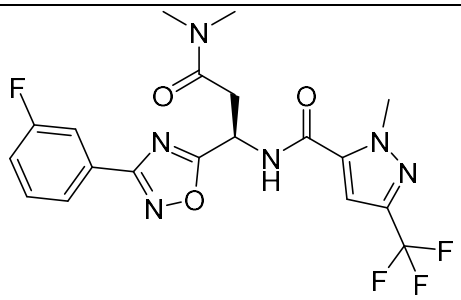
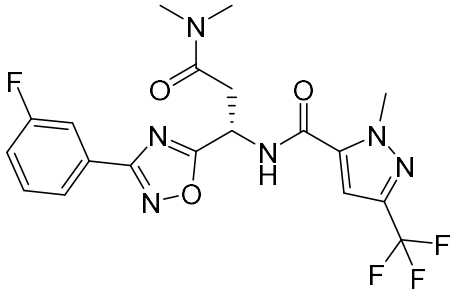
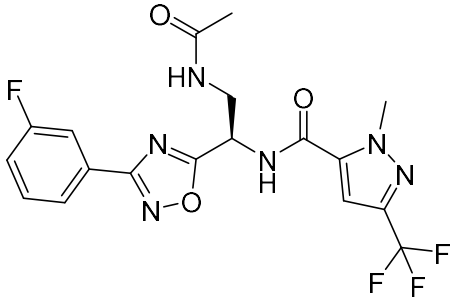
103	
104	
105	
106	
107	
108	

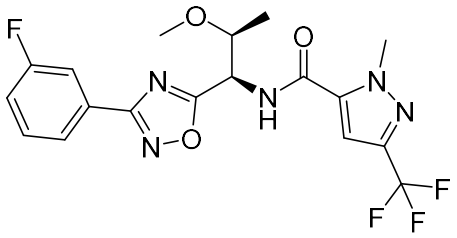
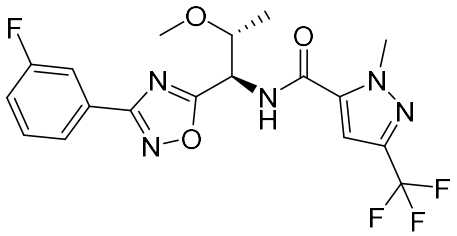
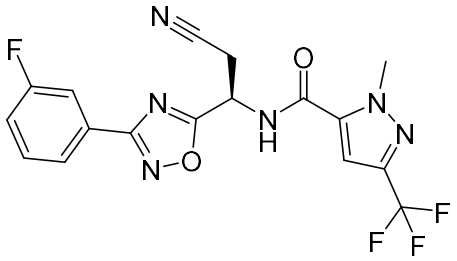
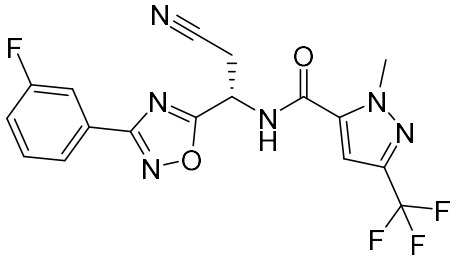
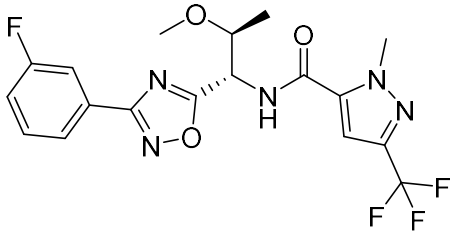
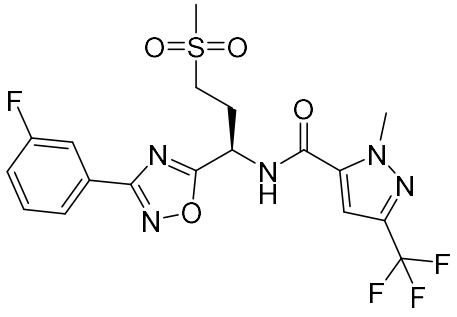
109	
110	
111	
112	
113	
114	

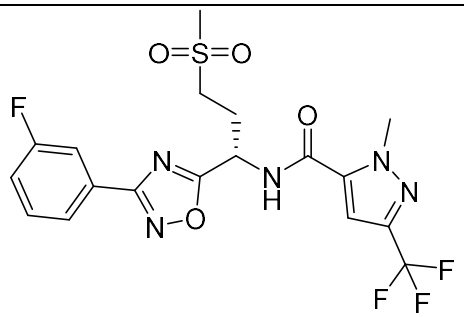
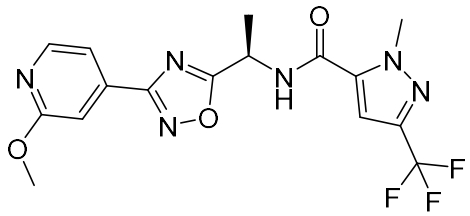
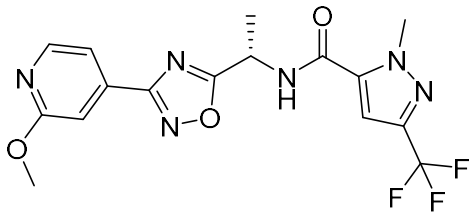
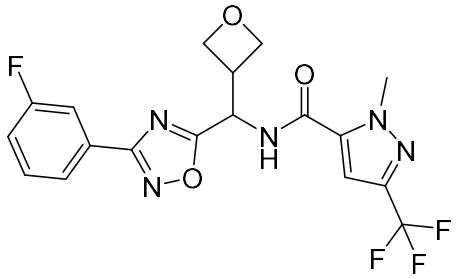
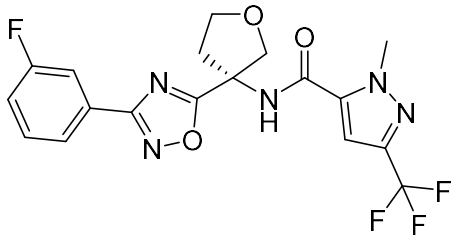
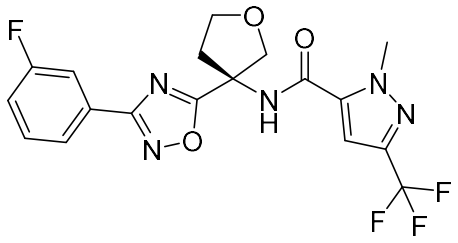
115	
116	
117	
118	
119	
120	

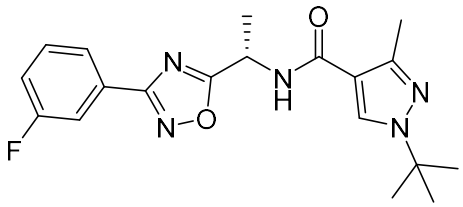
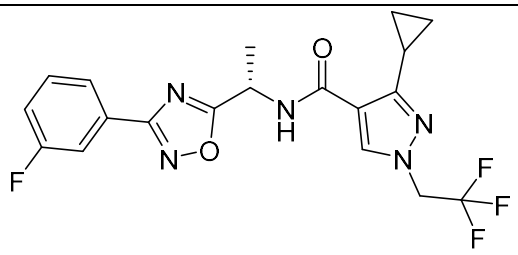
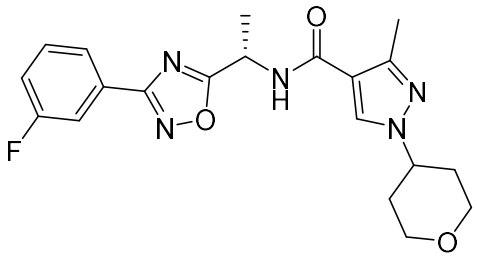
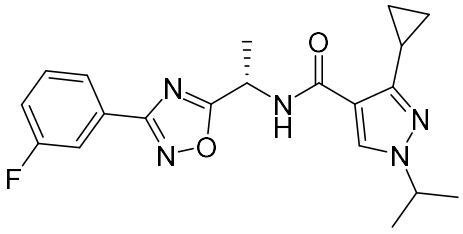
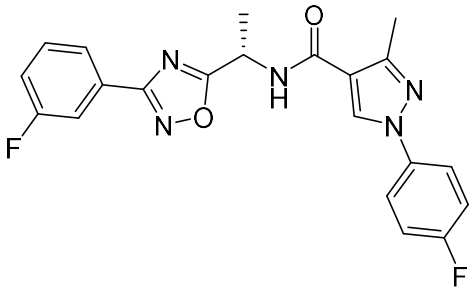
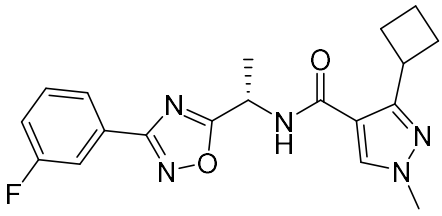
121	
122	
123	
124	
125	

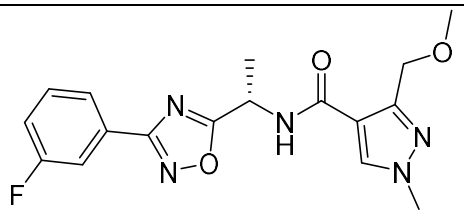
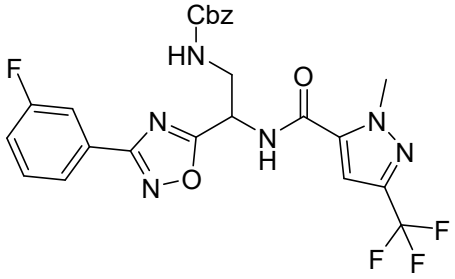
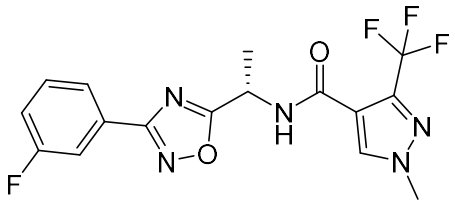
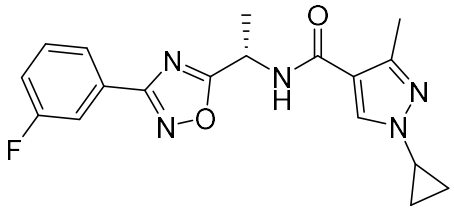
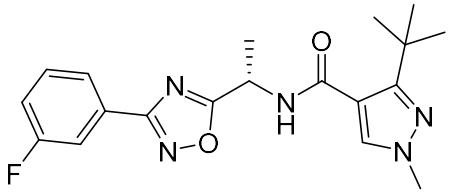
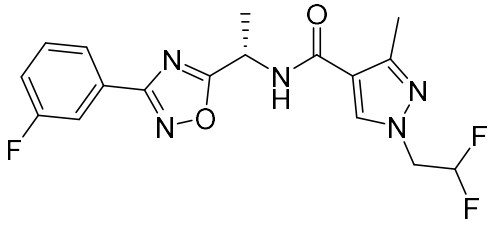
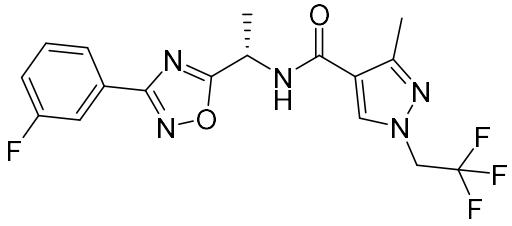
126	
127	
128	
129	
130	
131	

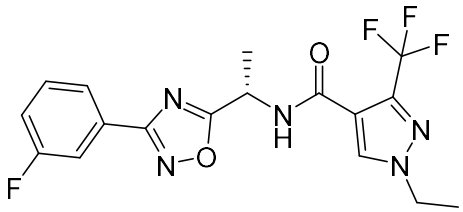
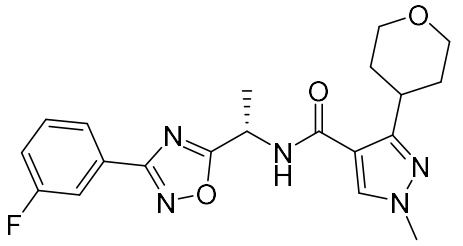
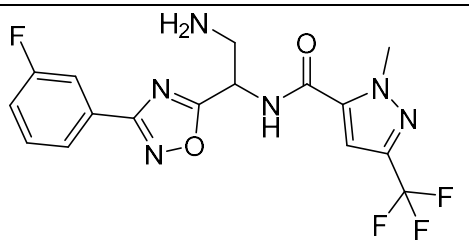
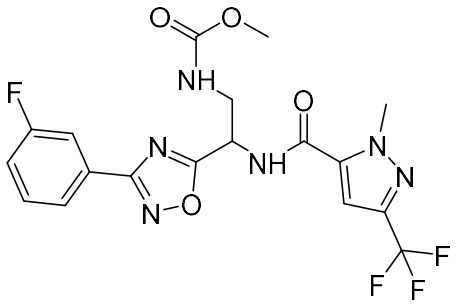
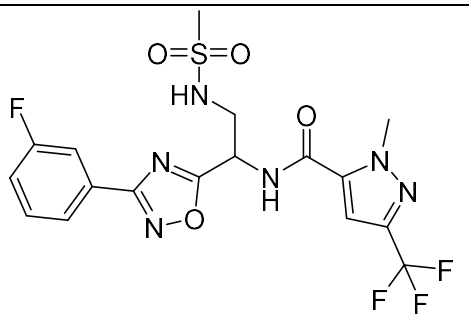
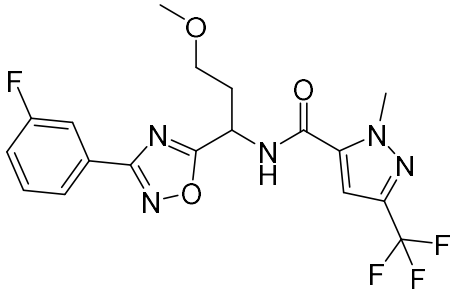
132	
133	
134	
135	
136	
137	

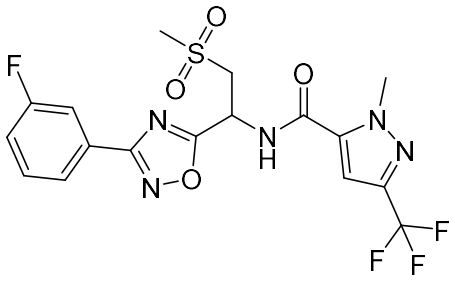
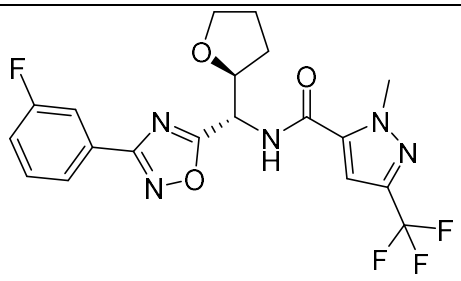
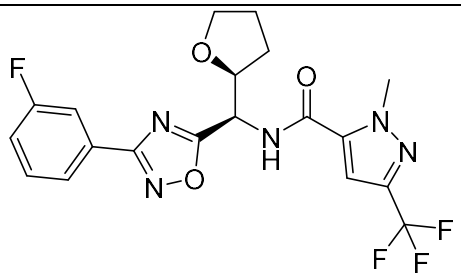
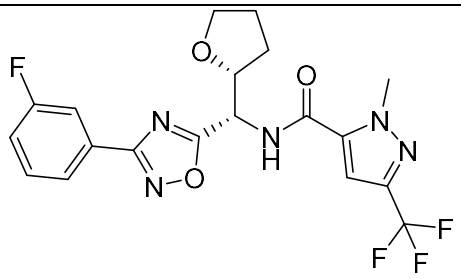
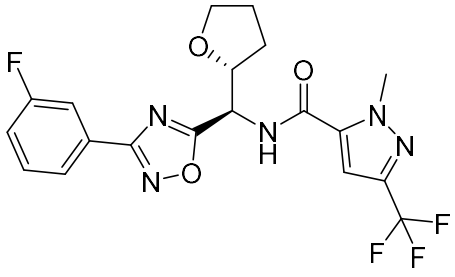
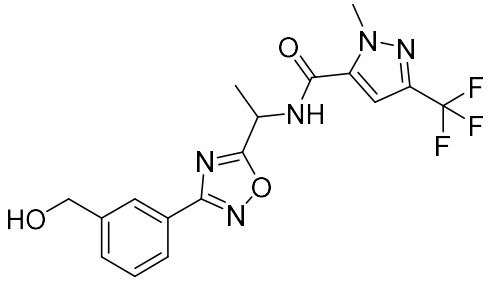
138	
139	
140	
141	
142	
143	

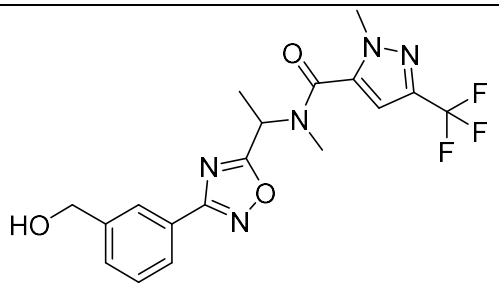
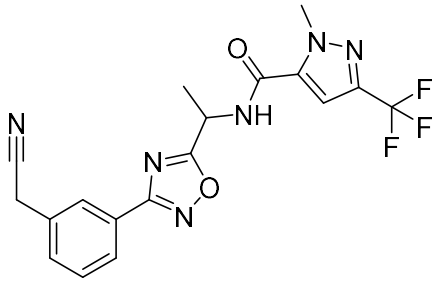
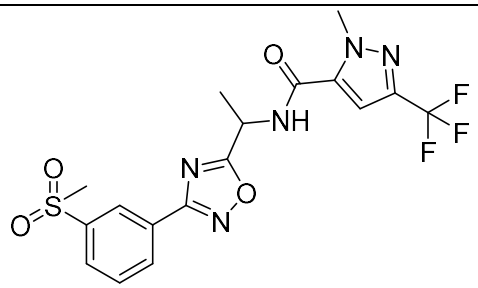
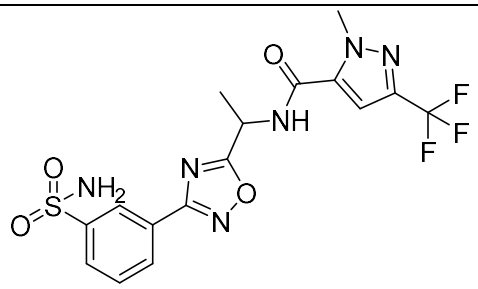
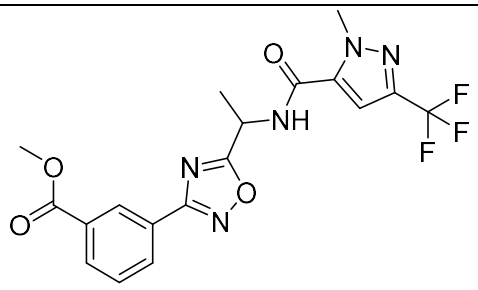
144	
145	
146	
147	
148	
149	

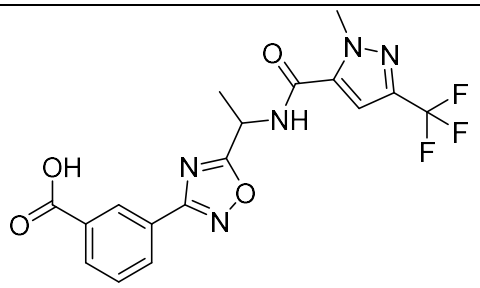
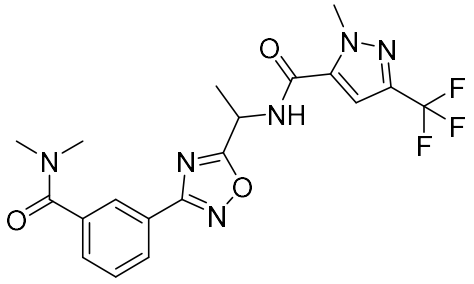
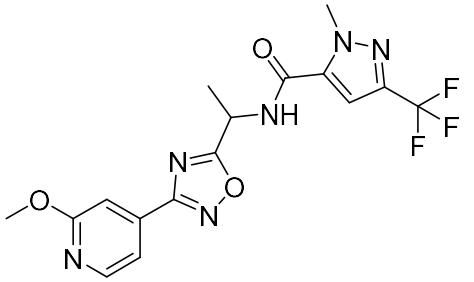
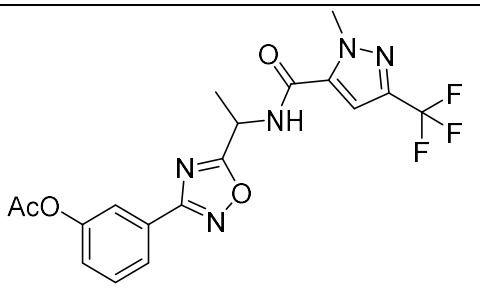
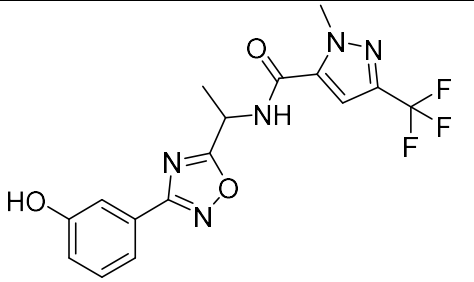
150	
151	
152	
153	
154	
155	

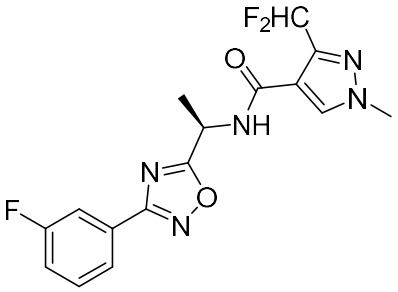
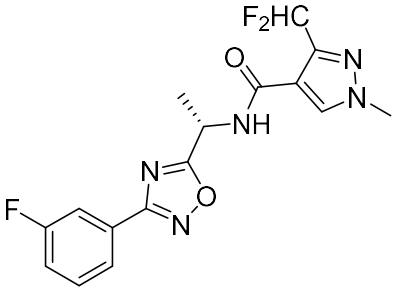
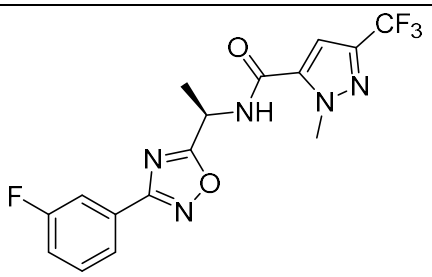
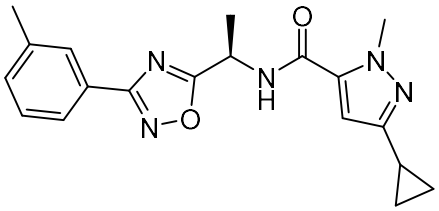
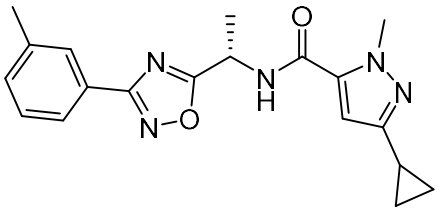
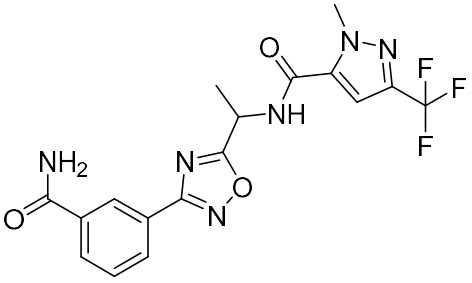
156	
157	
160	
161	
162	
163	
164	

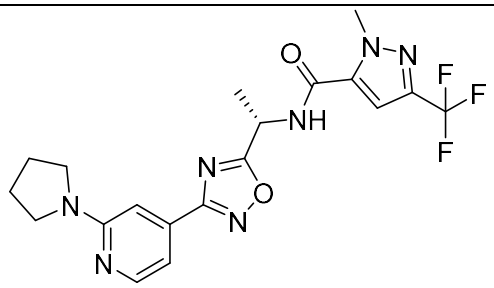
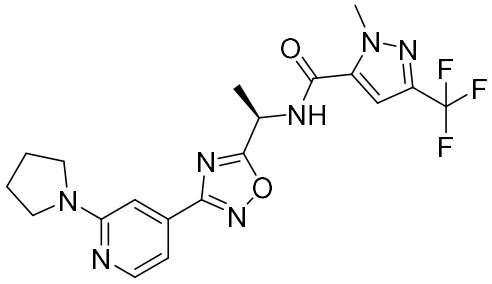
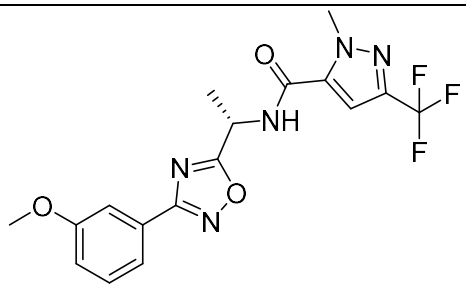
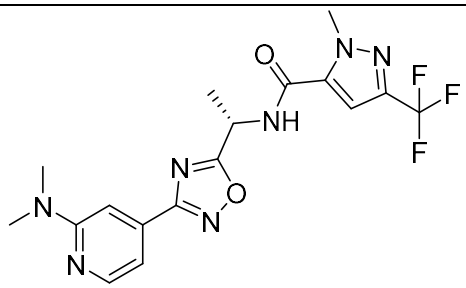
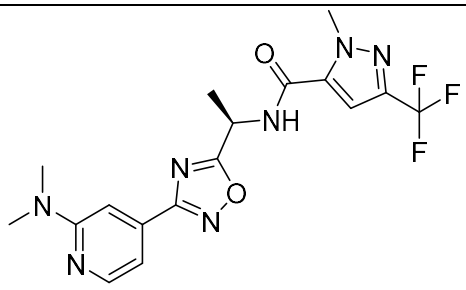
165	
166	
167	
168	
169	
170	

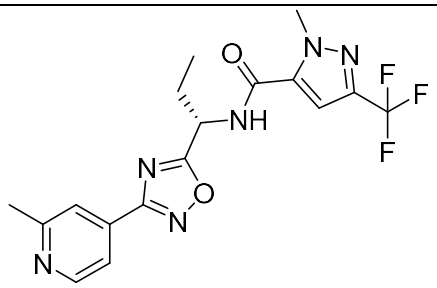
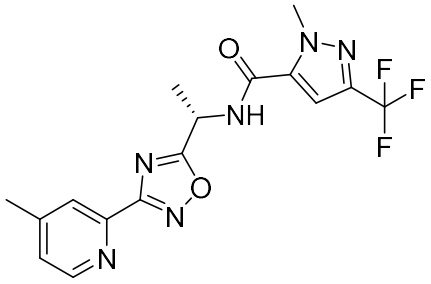
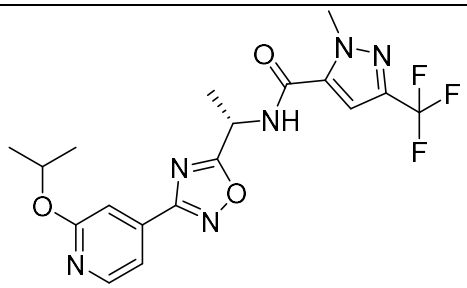
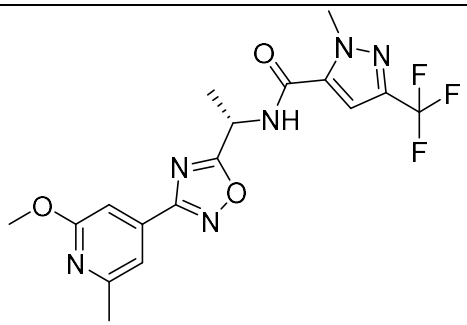
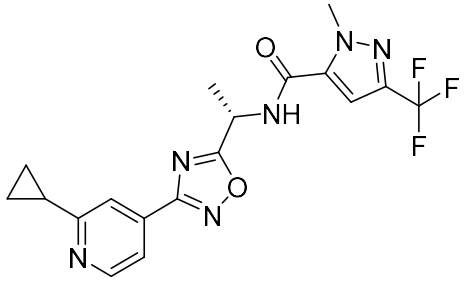
171	
172	
173	
174	
175	
176	

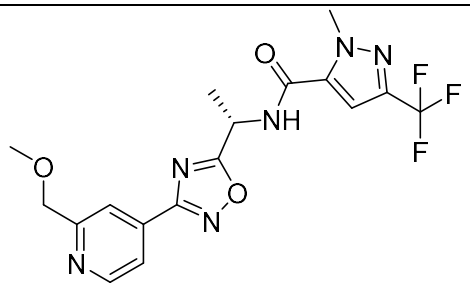
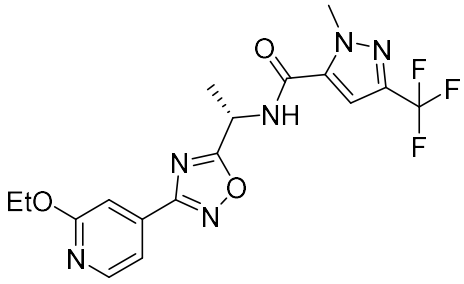
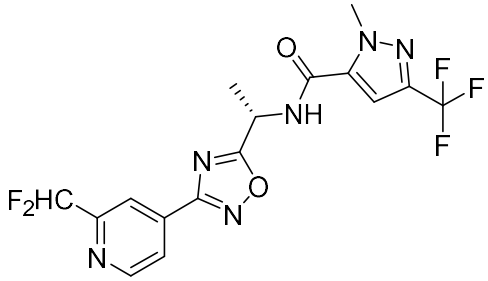
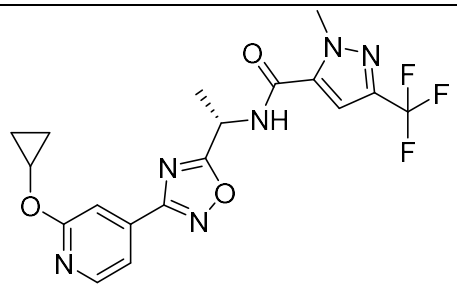
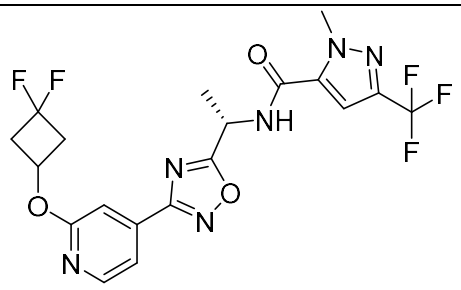
177	
178	
179	
180	
181	

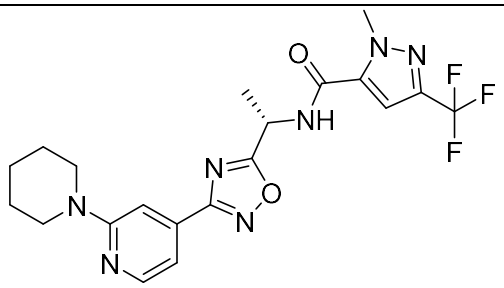
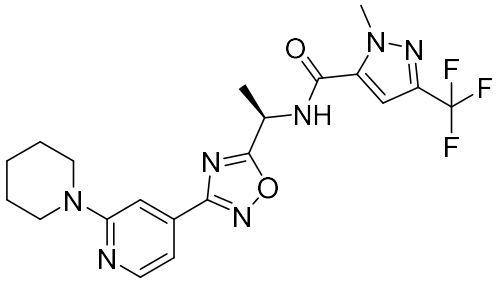
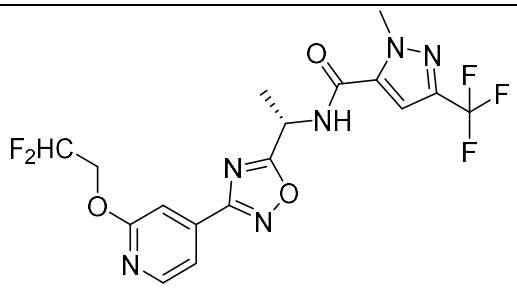
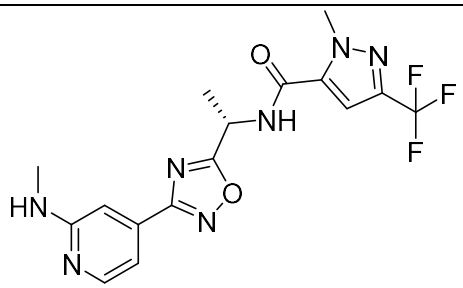
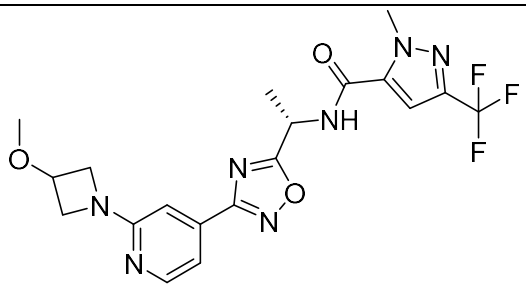
182	
183	
184	
185	
186	

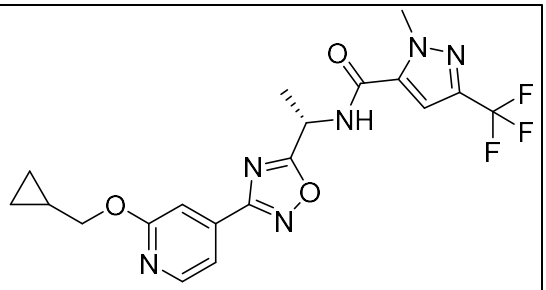
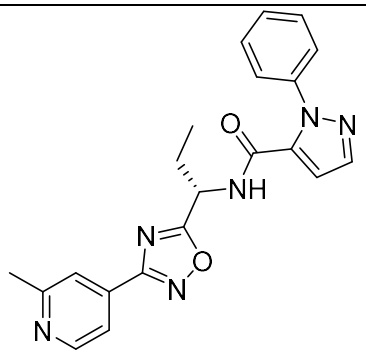
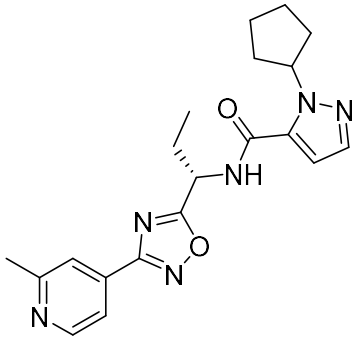
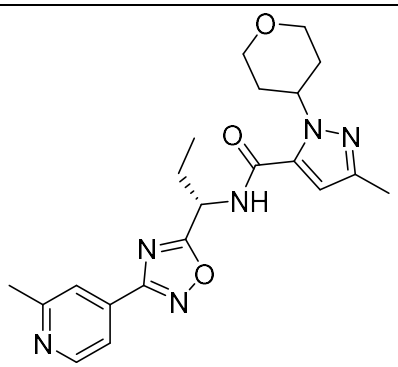
187	
188	
189	
191	
192	
193	

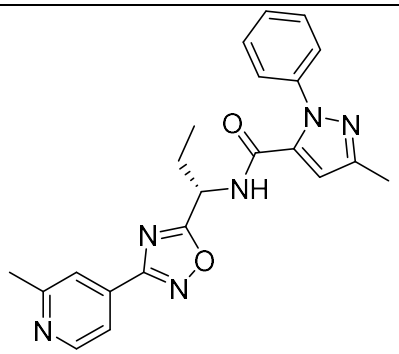
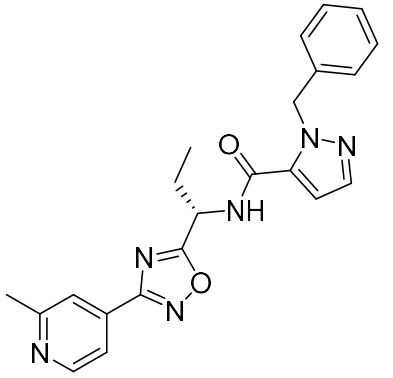
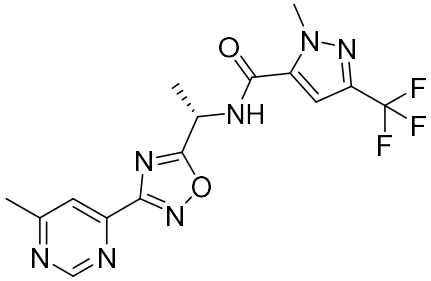
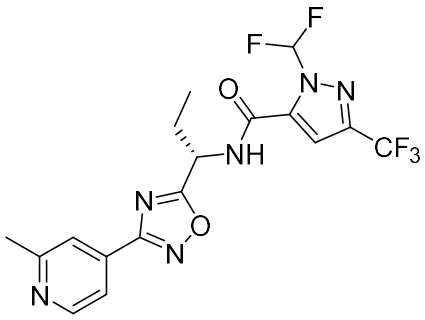
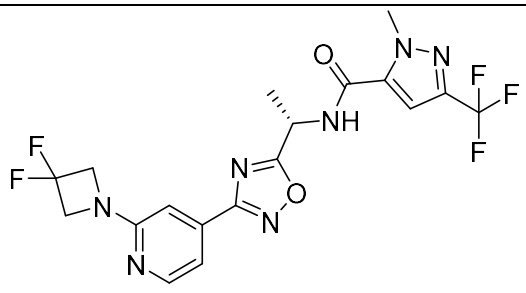
194	
195	
196	
197	
198	

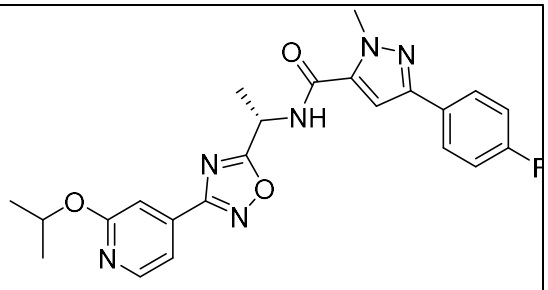
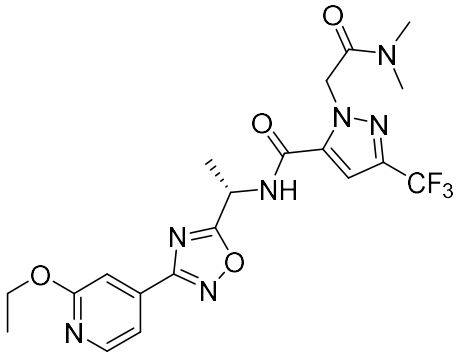
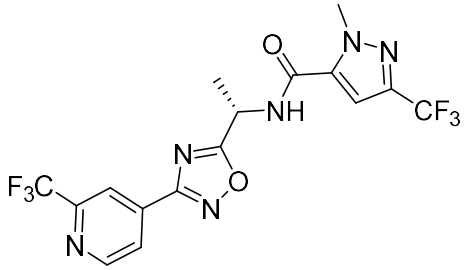
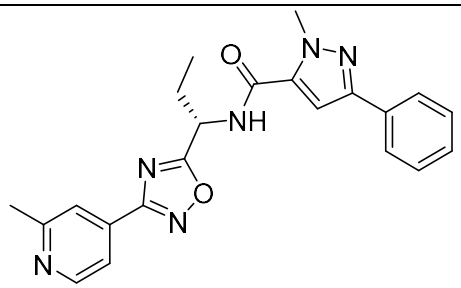
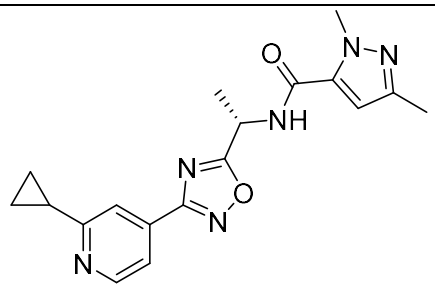
199	
200	
201	
202	
203	

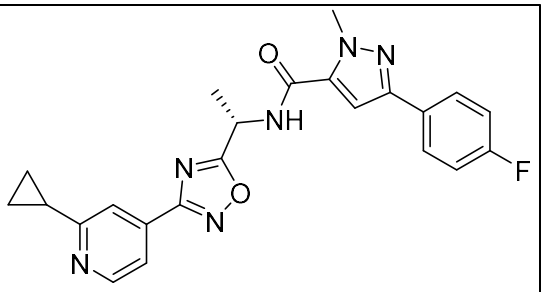
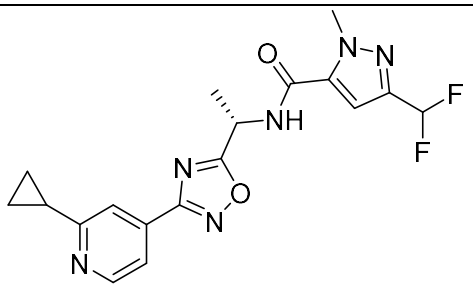
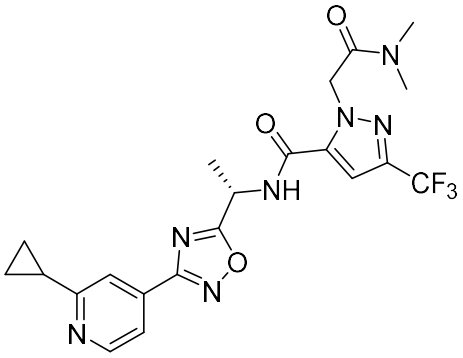
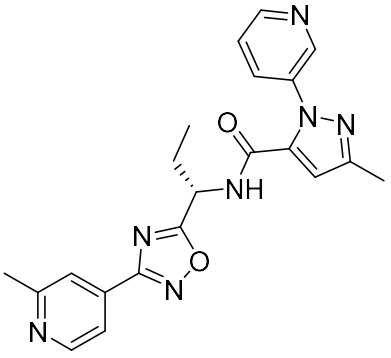
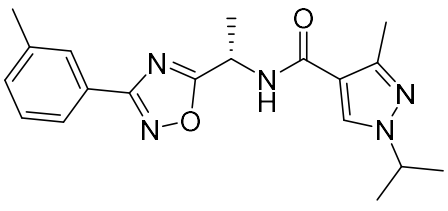
204	
205	
206	
207	
208	

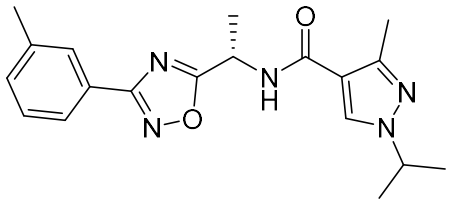
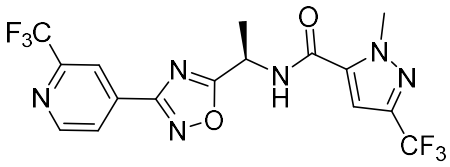
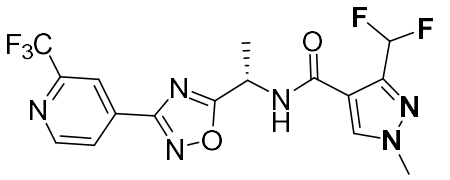
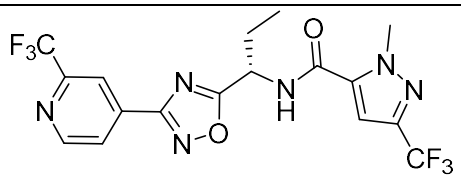
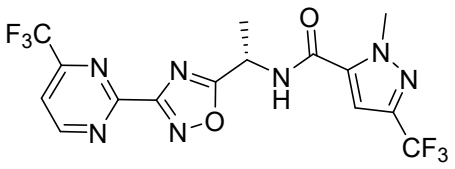
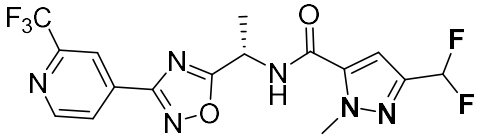
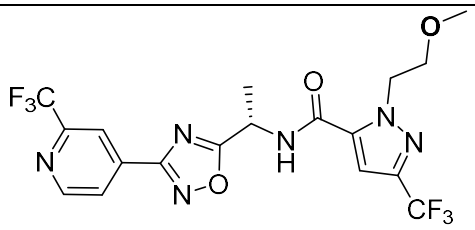
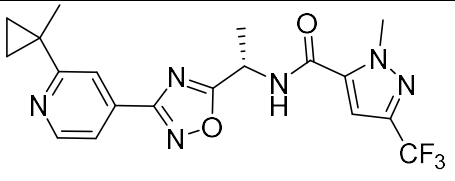
209	
210	
211	
212	
213	

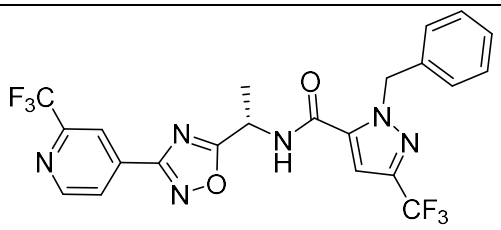
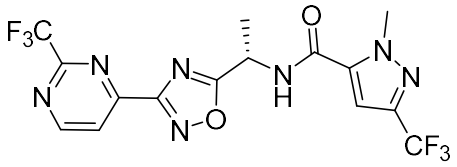
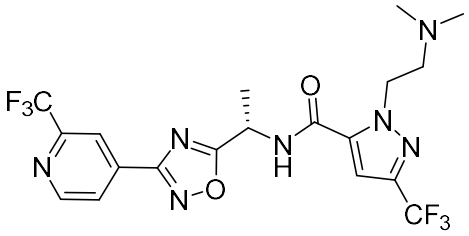
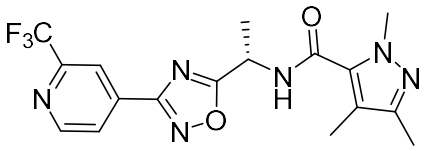
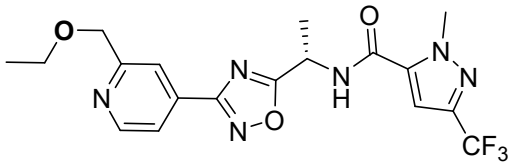
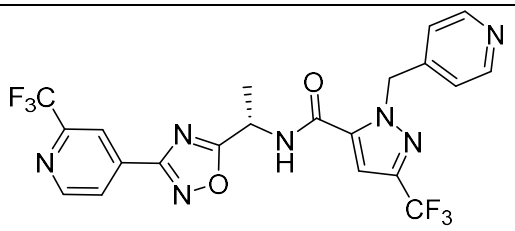
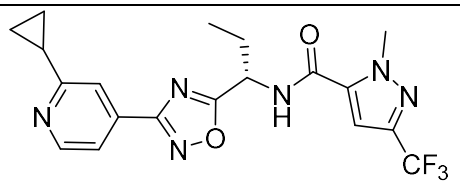
214	
215	
216	
217	

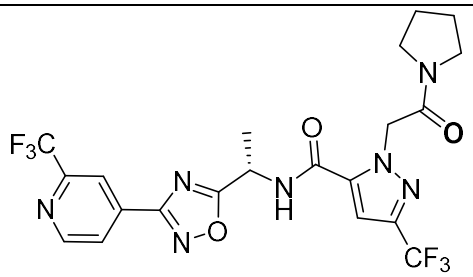
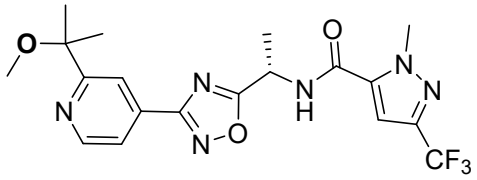
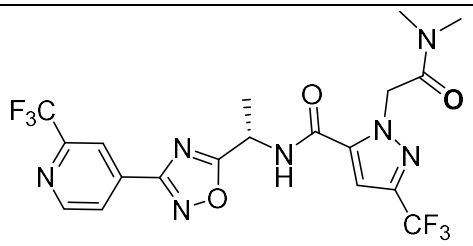
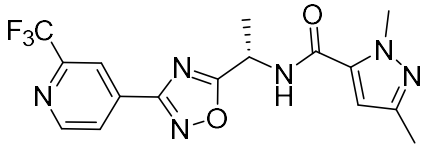
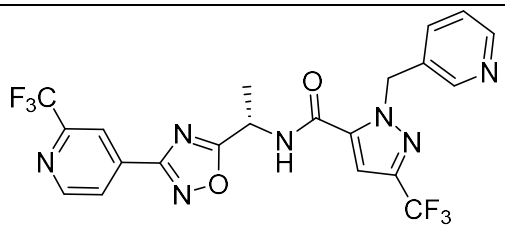
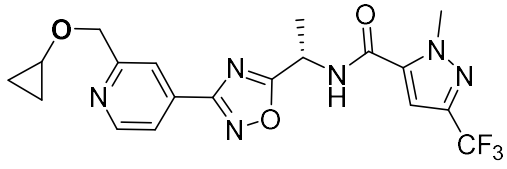
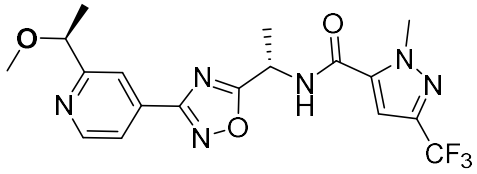
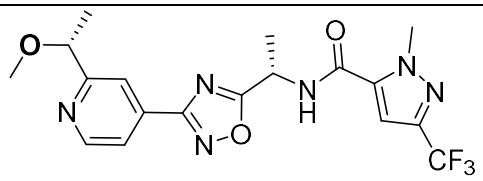
218	
219	
220	
221	
222	

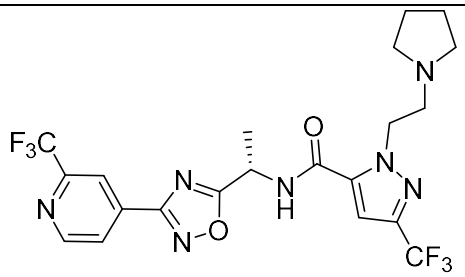
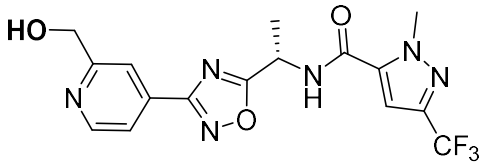
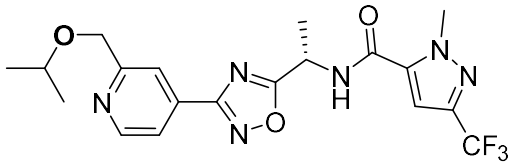
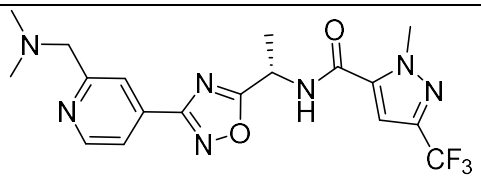
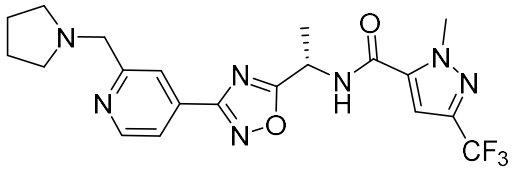
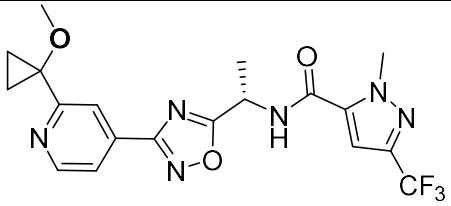
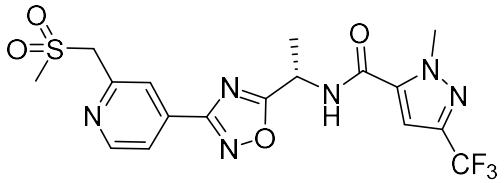
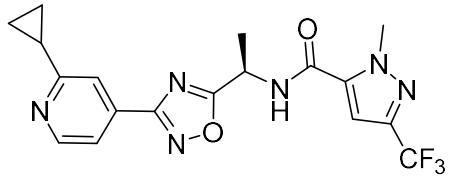
223	
224	
225	
226	
227	

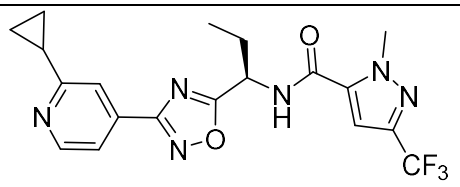
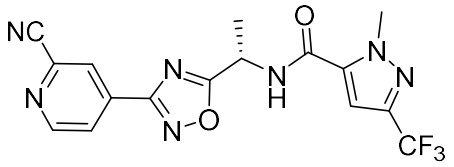
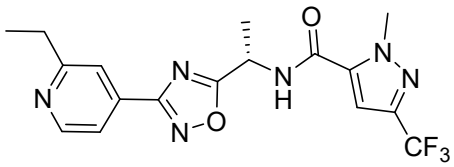
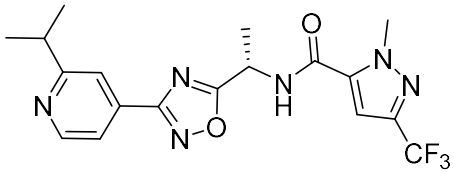
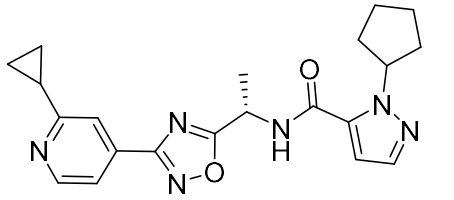
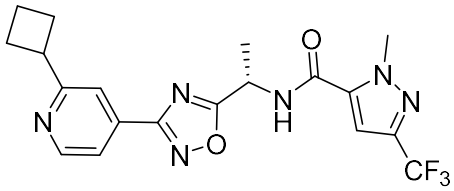
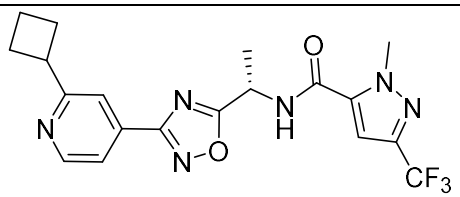
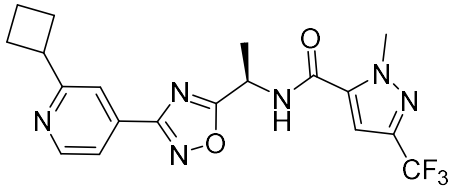
228	
229	
230	
231	
232	

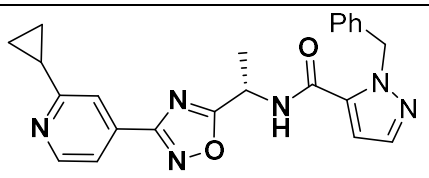
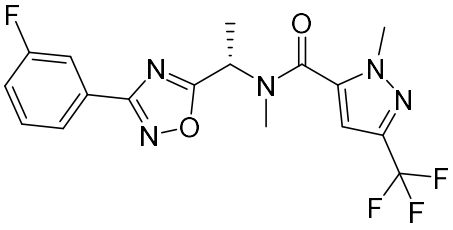
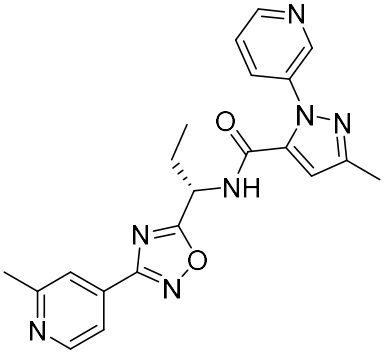
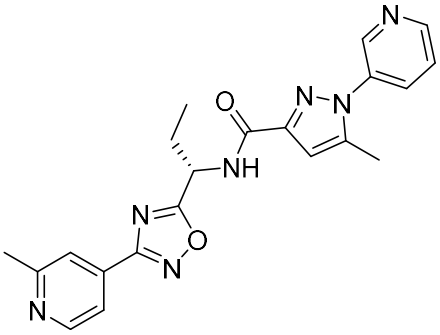
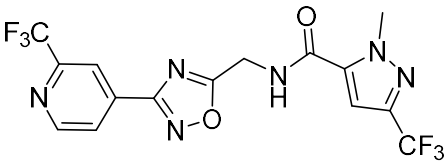
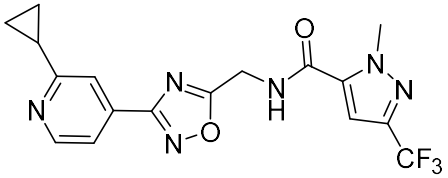
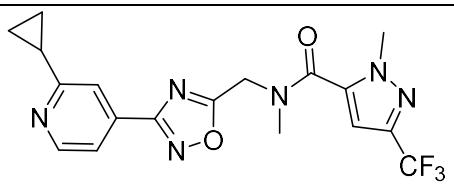
233	
234	
235	
236	
237	
238	
239	
240	

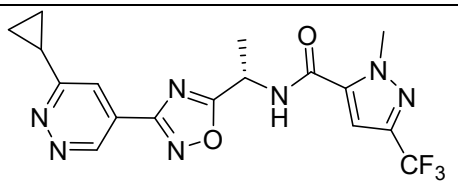
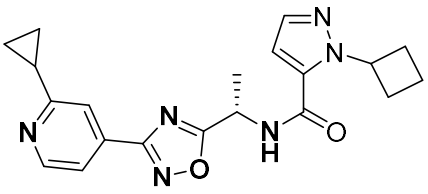
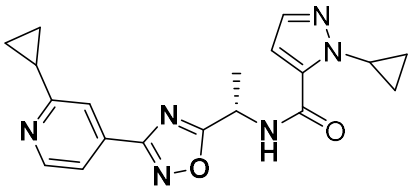
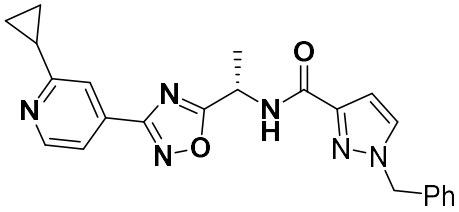
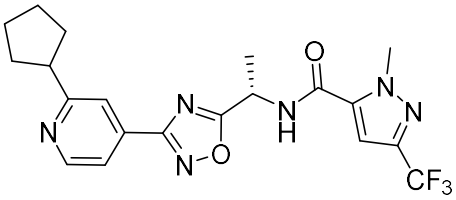
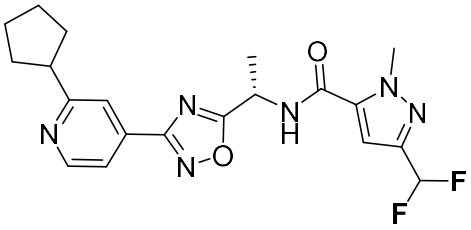
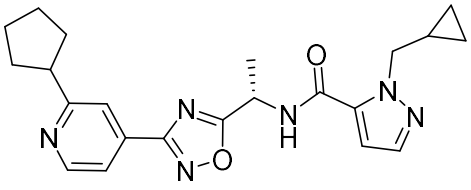
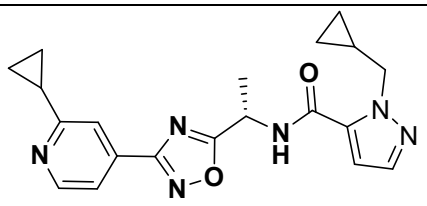
241	
242	
243	
244	
245	
246	
248	

249	
250	
251	
252	
253	
254	
255	
256	

257	
258	
259	
260	
261	
263	
264	
265	

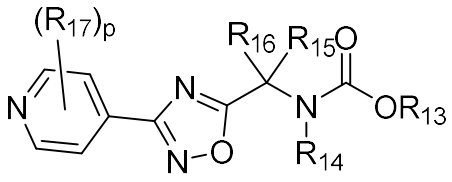
266	
267	
268	
269	
270	
271	
278	
279	

280	
297	
298	
299	
300	
301	
302	

303	
304	
305	
306	
307	
308	
309	
310	

, 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;

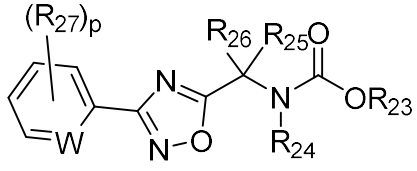
each R_{17} is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkylene-$N(R_{20})_2$, $C_{1\text{-}6}$alkylene-O-$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy optionally substituted with $C_{3\text{-}7}$cycloalkyl, $C_{1\text{-}6}$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;

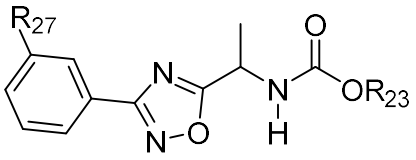
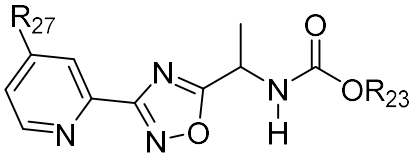
R_{19} is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, and $C_{3\text{-}10}$cycloalkyl; and

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

21. A pharmaceutical composition comprising a compound of Formula VII



(VII), wherein the compound is a compound of Formula **VII-a** or Formula **VII-b**:

 (**VII-a**),  (**VII-b**),

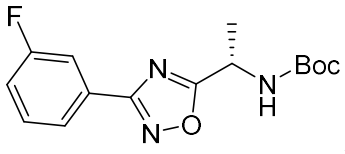
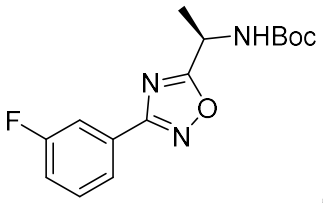
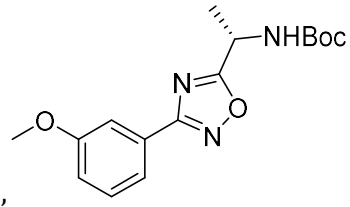
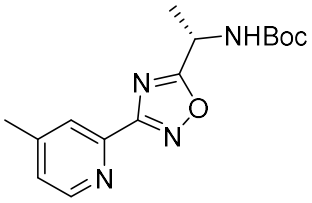
or a pharmaceutically acceptable salt thereof, wherein

R_{23} is a tert-butyl;

R_{24} is hydrogen;

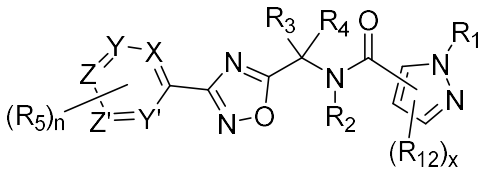
R_{25} is hydrogen; and

R_{27} is independently selected from the group consisting of halogen and $C_{1\text{-}6}$alkoxy; and a pharmaceutically acceptable excipient.

22. The pharmaceutical composition of claim 21, wherein the compound is selected from the group consisting of , , , and , or a pharmaceutically acceptable salt thereof.

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

24. 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 replaced 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.

25. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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.

26. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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.

27. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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.

28. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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).

29. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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 (SUDEP), Brugada syndrome, and myocardial infarction.

30. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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).

31. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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).

32. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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.

33. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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).

34. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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.

35. Use of a compound of any one of claims 15-20 or a pharmaceutical composition of any one of claims 1-14 and 21-23, 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), 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 (SUDEP), Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.