ION CHANNEL MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

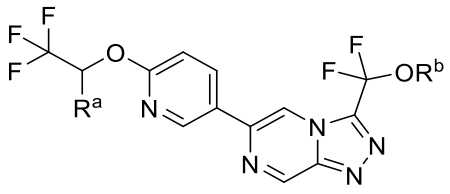
This application claims the benefit of U.S. Provisional Patent Application No. 62/940,500, filed November 26, 2019, the entire contents of which are incorporated by reference herein.

BACKGROUND

Sodium ion (Na+) channels primarily open in a transient manner and are quickly inactivated, thereby generating a fast Na+ current to initiate the action potential. The late or persistent sodium current (INaL) is a sustained component of the fast Na+ current of cardiac myocytes and neurons. Many common neurological and cardiac conditions are associated with abnormal INaL enhancement, which contributes to the pathogenesis of both electrical and contractile dysfunction in mammals (see, e.g., *Pharmacol Ther* (2008) 119:326-339). Accordingly, pharmaceutical compounds that selectively modulate sodium channel activity, e.g., abnormal INaL, are useful in treating such disease states.

SUMMARY

In one aspect of the present disclosure, there is provided a compound having the Formula **I**:



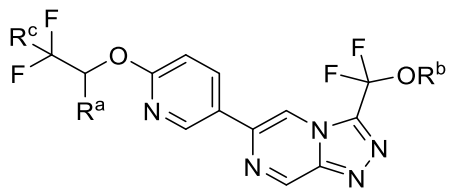
(**I**);

or a pharmaceutically acceptable salt thereof, wherein

R^a is C_{2-4} alkyl or monocyclic C_{3-6} cycloalkyl; and

R^b is C_{1-4} alkyl.

In another aspect of the present disclosure, there is provided a compound having the Formula **II**:



(**II**);

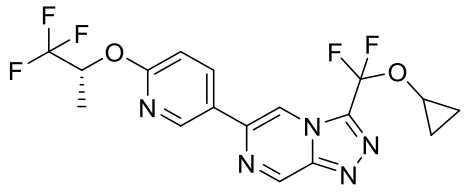
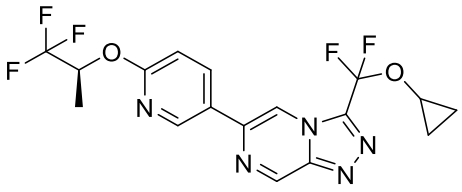
or a pharmaceutically acceptable salt thereof, wherein

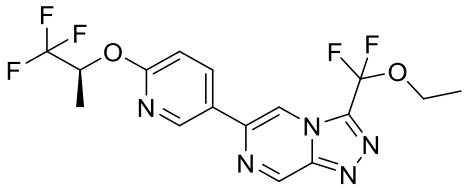
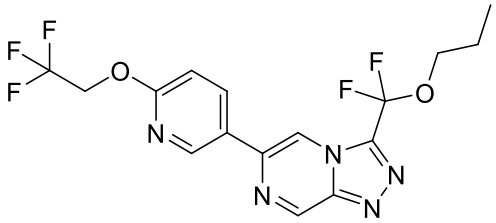
R^a is C_{1-4} alkyl;

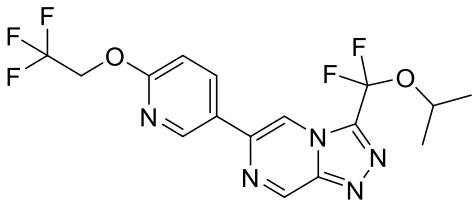
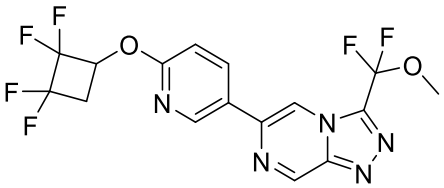
R^b is C_{1-4} alkyl; and

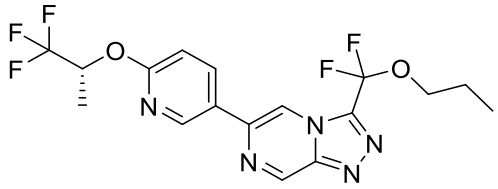
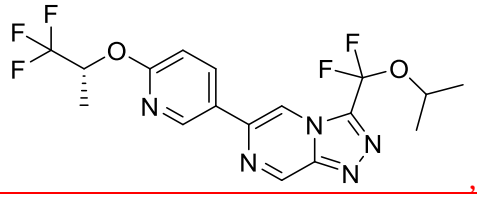
R^c is hydrogen or C_{1-4} alkyl.

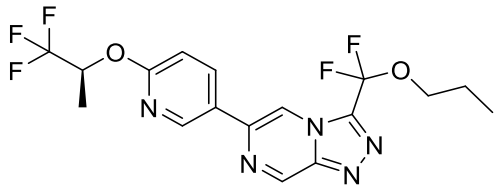
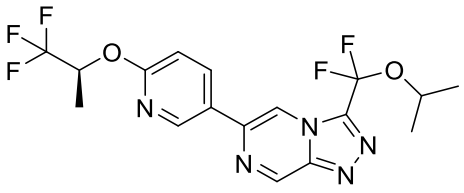
In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:


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, and 
or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a condition relating to aberrant function of a sodium ion channel.

In another aspect of the present disclosure, there is provided a use of the compound disclosed herein, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a neurological disorder or a psychiatric disorder.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a pain.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, wherein the TAC is selected from the group consisting of paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a migraine in a subject in need thereof, wherein the migraine is selected from the group consisting of migraine without aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM).

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical

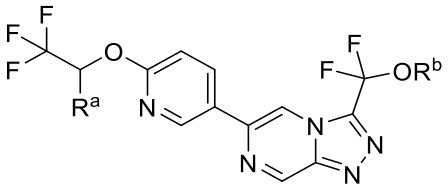
composition disclosed herein, in the manufacture of a medicament for treating or preventing cortical spreading depression (CSD).

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a cranial neuropathy or multiple cranial neuropathies, wherein the cranial neuropathy is selected from the group consisting of bell palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

Described herein are fused heteroaryl compounds and compositions useful for preventing and/or treating a disease, disorder, or condition, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, e.g., abnormal late/persistent sodium current (INaL).

Thus, in one ~~aspect~~example, provided herein is a compound having the Formula **I**:

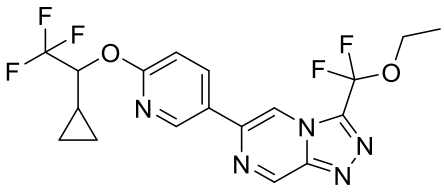
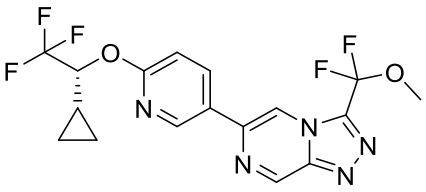
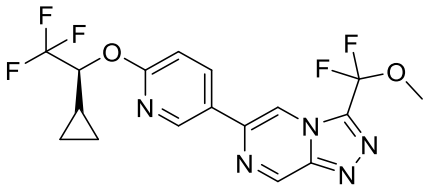
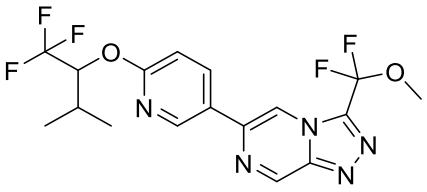
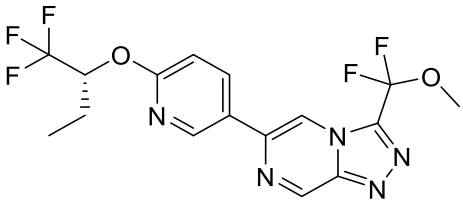
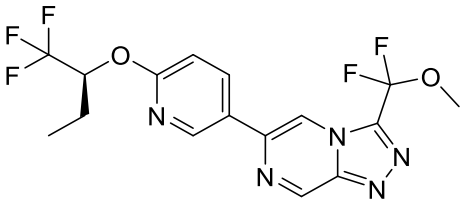
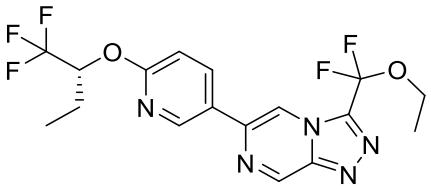
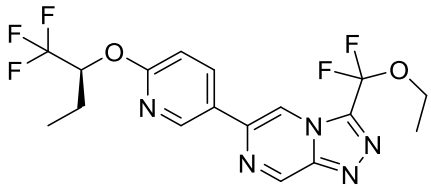
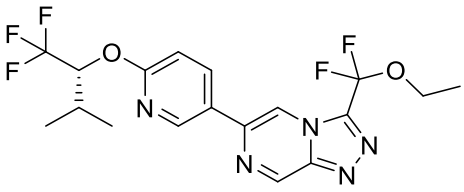
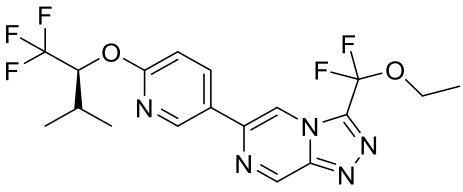
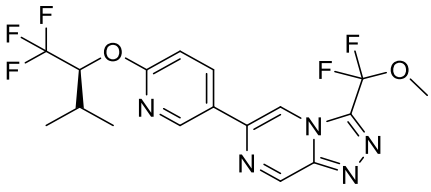
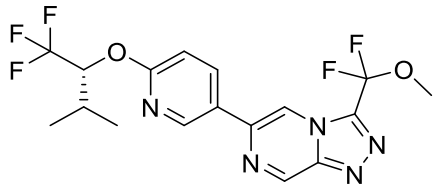
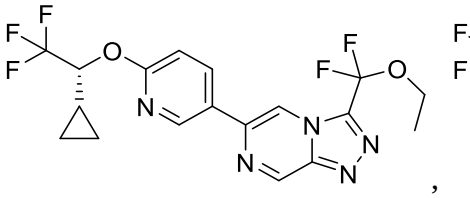
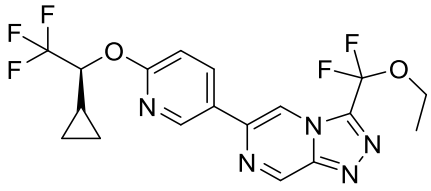
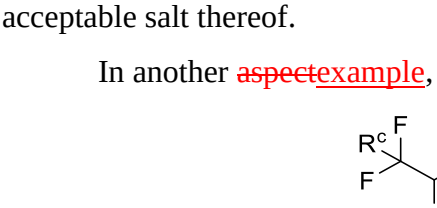
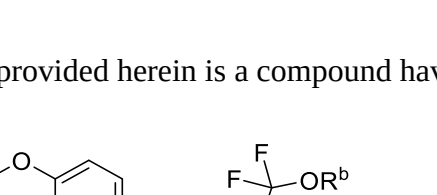


(**I**);

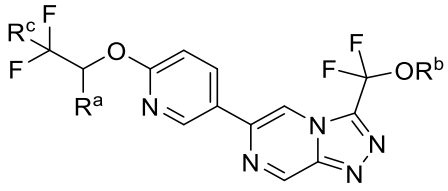
or a pharmaceutically acceptable salt thereof, wherein R^a is $C_{2\text{-}4}$alkyl or monocyclic $C_{3\text{-}6}$ cycloalkyl; and R^b is $C_{1\text{-}4}$alkyl.

In some ~~embodiment~~examples, R^a is ethyl, isopropyl, or cyclopropyl. In some ~~embodiment~~examples, R^b is methyl or ethyl.

In some ~~embodiment~~examples, the compound of Formula **I** is selected from the group consisting of:


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, or a pharmaceutically acceptable salt thereof.

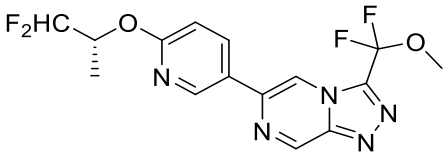
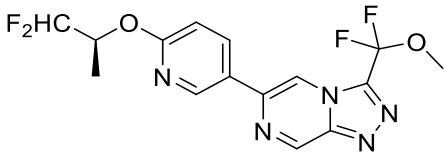
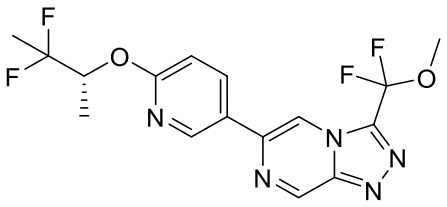
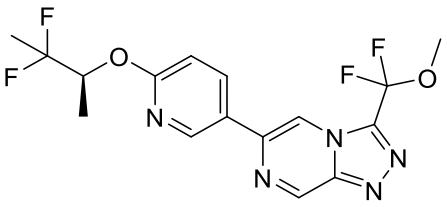
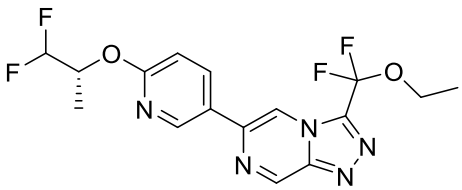
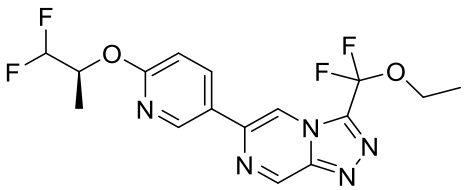
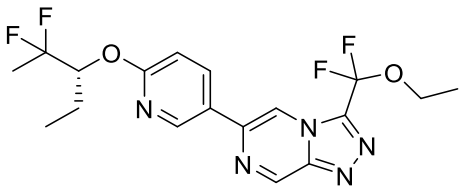
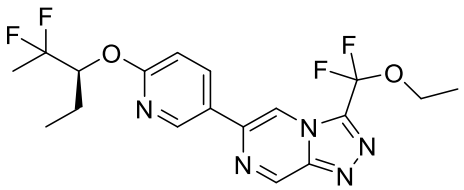
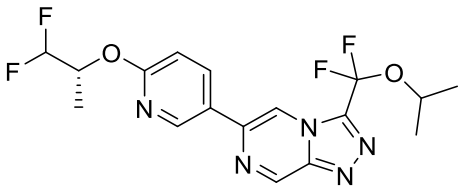
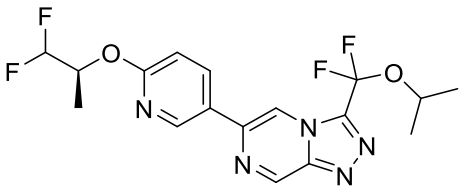
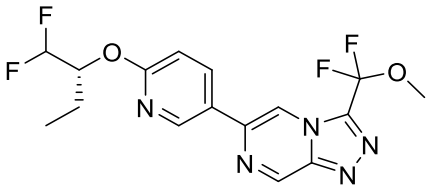
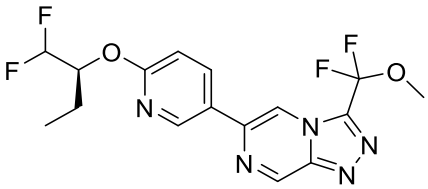
In another ~~aspect~~example, provided herein is a compound having the Formula **II**:


(**II**);

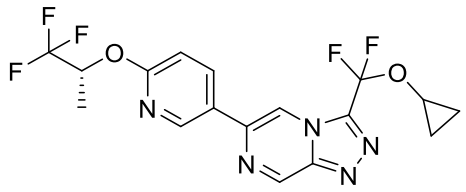
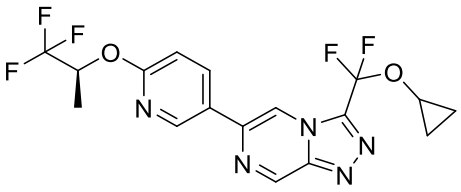
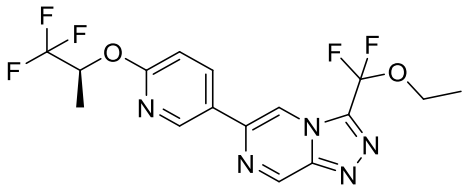
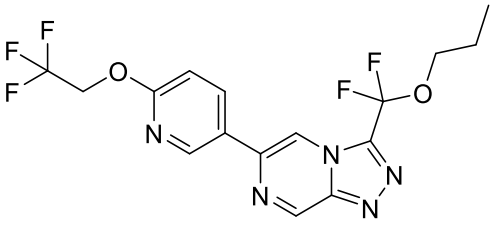
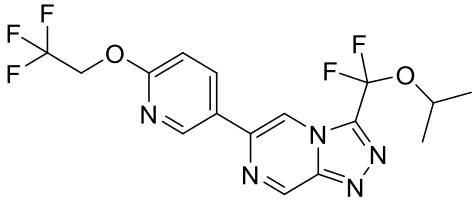
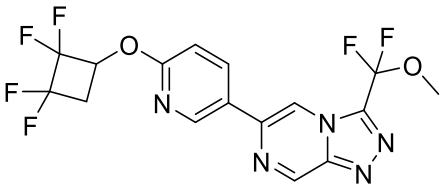
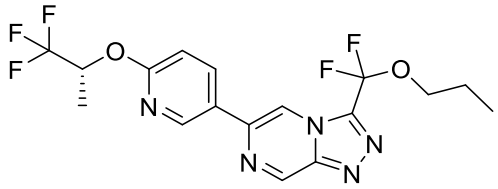
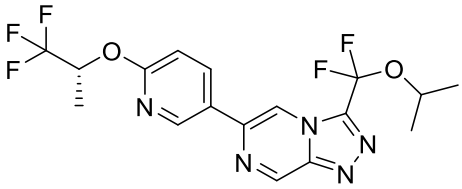
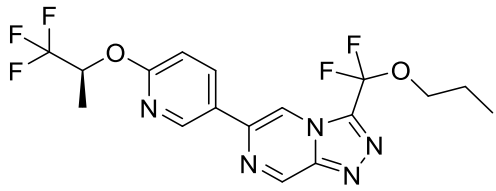
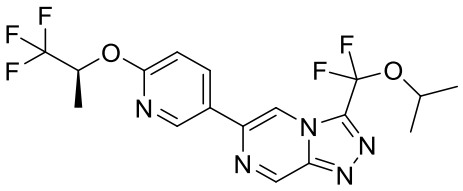
or a pharmaceutically acceptable salt thereof, wherein R^a is C_{1-4}alkyl; R^b is C_{1-4}alkyl; and R^c is hydrogen or C_{1-4}alkyl.

In some ~~embodiment~~examples, R^a is methyl. In some ~~embodiment~~examples, R^a is methyl or ethyl. In some ~~embodiment~~examples, R^b is methyl. In some ~~embodiment~~examples, R^b is methyl, ethyl, or isopropyl. In some ~~embodiment~~examples, R^c is hydrogen or methyl. In some ~~embodiment~~examples, R^c is hydrogen. In some ~~embodiment~~examples, R^c is methyl.

In some ~~embodiment~~examples, the compound of Formula **II** is selected from the group consisting of:


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, or a pharmaceutically acceptable salt thereof.

In another ~~aspect~~example, provided herein is a compound selected from the group consisting of:


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, and

or a pharmaceutically acceptable salt thereof.

Also provided herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In one ~~aspect~~example, provided herein is a method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In some ~~embodiment~~examples, the condition is a neurological or psychiatric disorder. In some ~~embodiment~~examples, the condition is epilepsy or an epilepsy syndrome. In some ~~embodiment~~examples, the condition is a genetic epilepsy or a genetic epilepsy syndrome. In some

~~embodiment~~examples, the condition is a pediatric epilepsy or a pediatric epilepsy syndrome. In some ~~embodiment~~examples, the condition is epileptic encephalopathy. In some ~~embodiment~~examples, the epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome.

In some ~~embodiment~~examples, the condition is selected from the group consisting of epileptic encephalopathy, 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.

In another ~~aspect~~example, the present ~~invention~~disclosure discloses a method of treating a neurological disorder or a psychiatric disorder, wherein the method comprises administering to a subject in need thereof the compound described herein, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In another ~~aspect~~example, provided herein is a method of treating a pain, wherein the method comprises administering to a subject in need thereof a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In another ~~aspect~~example, methods of preventing or treating trigeminal autonomic cephalalgia (*e.g.*, paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania) are provided. Also provided herein are methods of preventing or treating a cranial neuropathy (*e.g.*, bell palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy) or multiple cranial neuropathies (MCN). In certain ~~embodiment~~examples, methods of preventing or treating a migraine (*e.g.*, migraine without aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM)) are provided. In some other

~~embodiment~~example**s**, provided herein are methods of preventing or treating cortical spreading depression (CDC).

In one ~~aspect~~example, the present disclosure provides a method of treating or preventing trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein, wherein the TAC is selected from the group consisting of paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania.

In another ~~aspect~~example, provided herein is a method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein, wherein the migraine is selected from the group consisting of migraine without aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM).

In another ~~aspect~~example, the present disclosure provides a method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In another ~~aspect~~example, the present disclosure provides a method of treating or preventing a cranial neuropathy or multiple cranial neuropathies (MCN) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

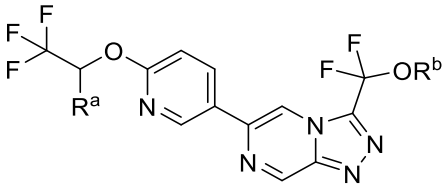
Other objects and advantages will become apparent to those skilled in the art from consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

DETAILED DESCRIPTION

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 relating to aberrant function of a sodium ion channel, such as abnormal late sodium current (INaL). Exemplary diseases, disorders, or

CLAIMS

1. A compound having the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

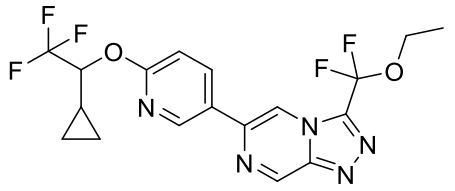
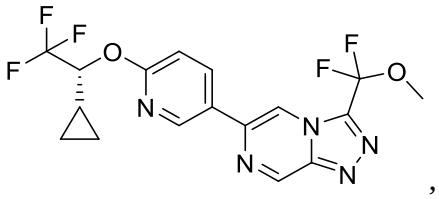
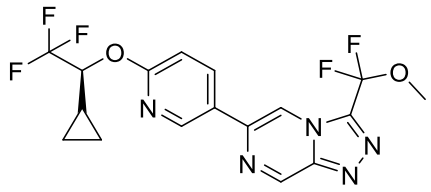
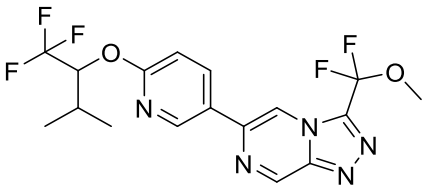
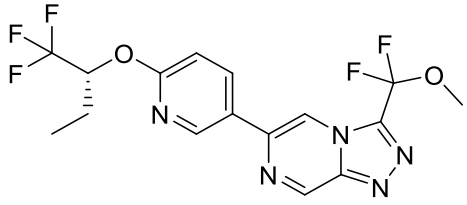
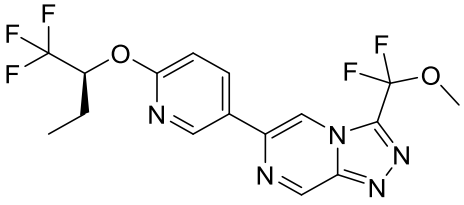
R^a is C_{2-4} alkyl or monocyclic C_{3-6} cycloalkyl; and

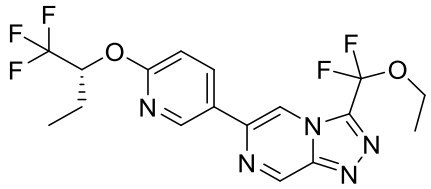
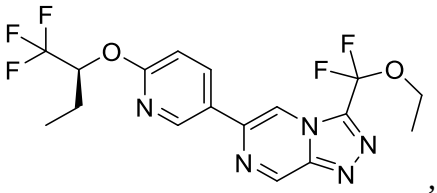
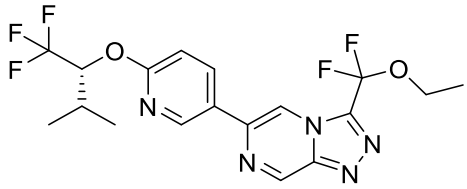
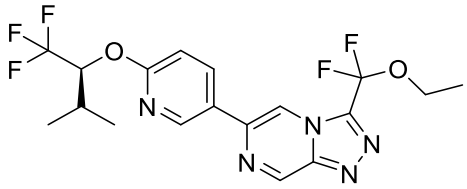
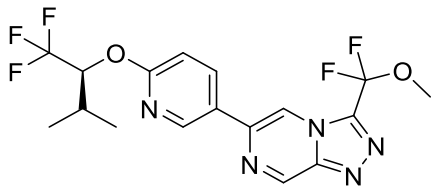
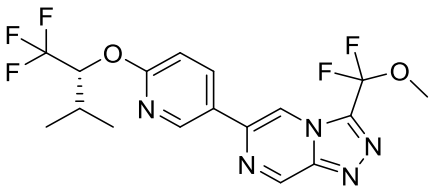
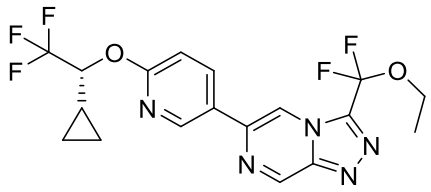
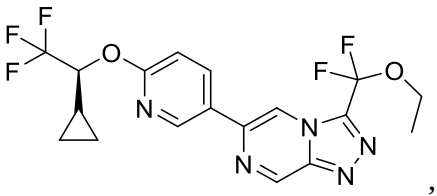
R^b is C_{1-4} alkyl.

2. The compound of claim 1, wherein R^a is ethyl, isopropyl, or cyclopropyl.

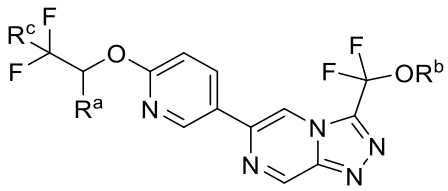
3. The compound of claim 1 or 2, wherein R^b is methyl or ethyl.

4. The compound of claim 1, wherein the compound is selected from the group consisting of:


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, or a pharmaceutically acceptable salt thereof.

5. A compound having the Formula **II**:


(**II**);

or a pharmaceutically acceptable salt thereof, wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl; and

R^c is hydrogen or C_{1-4} alkyl.

6. The compound of claim 5, wherein R^a is methyl or ethyl.

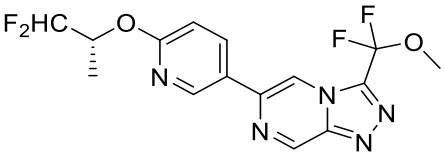
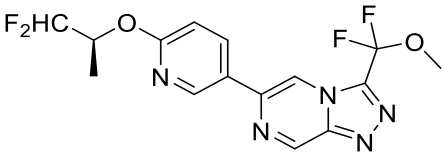
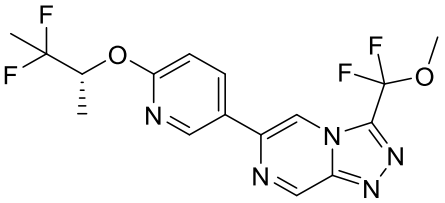
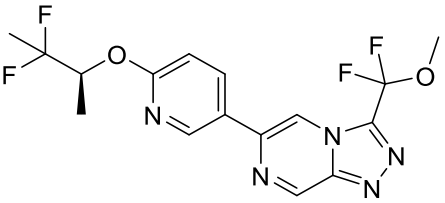
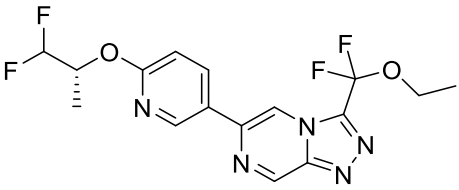
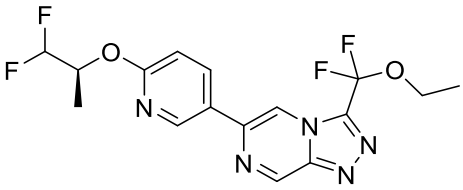
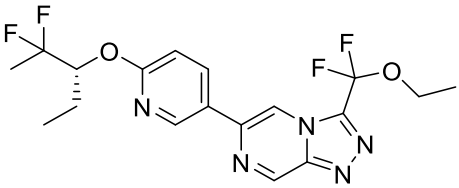
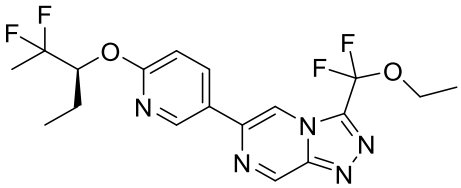
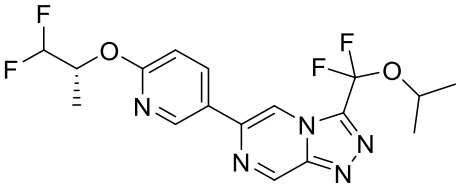
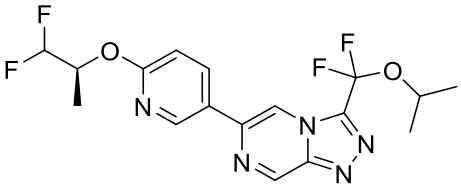
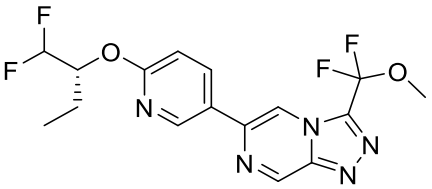
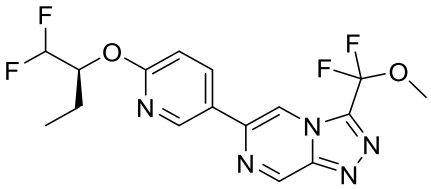
7. The compound of claim 5 or 6, wherein R^b is methyl, ethyl, or isopropyl.

8. The compound of any one of claims 5-7, wherein R^c is hydrogen or methyl.

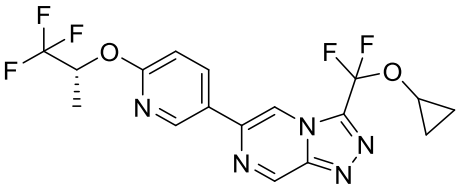
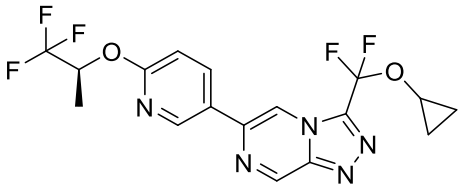
9. The compound of any one of claims 5-8, wherein R^c is hydrogen.

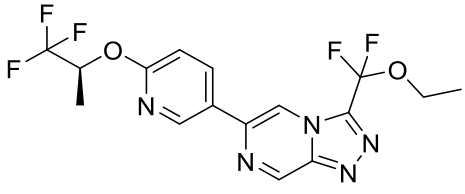
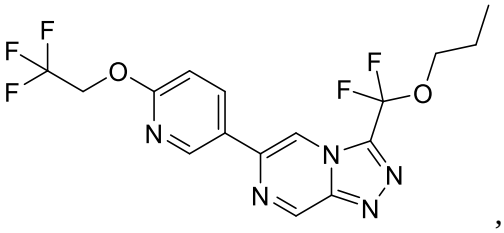
10. The compound of any one of claims 5-8, wherein R^c is methyl.

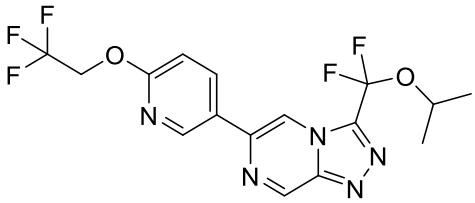
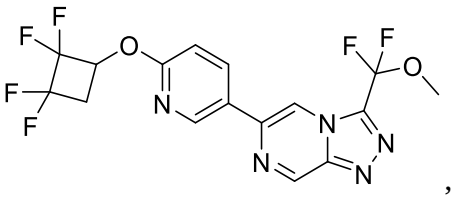
11. The compound of claim 5, wherein the compound is selected from the group consisting of:

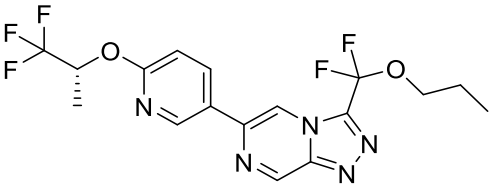
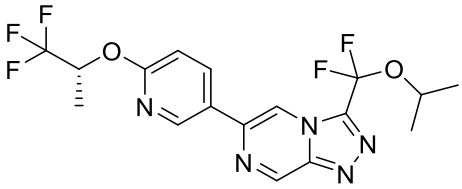

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, or a pharmaceutically acceptable salt thereof.

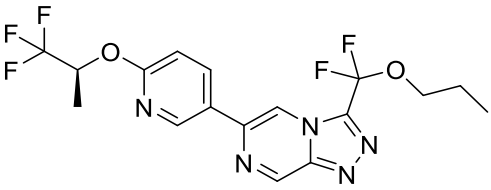
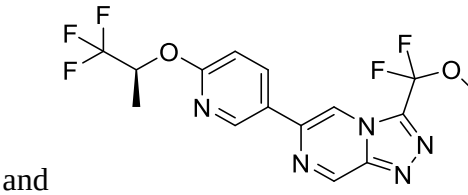
12. A compound selected from the group consisting of:

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, and or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

14. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating a condition relating to aberrant function of a sodium ion channel ~~in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~.

15. The ~~method~~use of claim 14, wherein the condition is a neurological or psychiatric disorder.

16. The ~~method~~use of claim 14 or 15, wherein the condition is epilepsy or an epilepsy syndrome.

17. The ~~method~~use of any one of claims 14-16, wherein the condition is selected from the group consisting of: a genetic epilepsy~~, or~~ a genetic epilepsy syndrome, a pediatric epilepsy, a pediatric epilepsy syndrome and epileptic encephalopathy.

~~18. The method of any one of claims 14-16, wherein the condition is a pediatric epilepsy or a pediatric epilepsy syndrome.~~

~~19. The method of any one of claims 14-16, wherein the condition is epileptic encephalopathy.~~

~~20~~18. The ~~method~~use of claim ~~19~~17, wherein the epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome.

~~21~~19. The ~~method~~use of claim 14 or 15, wherein the condition is selected from the group consisting of epileptic encephalopathy, 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.

~~22~~20. Use of the compound of any one of claims 1-12, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating a neurological disorder or a psychiatric disorder~~, wherein the method comprises administering to a subject in need thereof the compound of~~

~~any one of claims 1-12, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~.

~~23~~21. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating a pain~~, wherein the method comprises administering to a subject in need thereof a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~.

~~24~~22. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof~~, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~, wherein the TAC is selected from the group consisting of paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania.

~~25~~23. The ~~method~~use of claim ~~24~~22, wherein the TAC is a short-lasting unilateral neuralgiform headache attack.

~~26~~24. The ~~method~~use of claim ~~24~~22 or ~~25~~23, wherein the TAC is SUNCT or SUNA.

~~27. The method of claim 24 or 25, wherein the TAC is SUNA.~~

~~28~~25. The ~~method~~use of any one of claims ~~24~~22-~~27~~24, wherein the subject has an inadequate response to at least one medication used for the treatment of a TAC.

~~29~~26. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating or preventing a migraine in a subject in need thereof~~, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~, wherein the migraine is selected from the group consisting of migraine without

aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM).

~~30~~27. The ~~method~~use of claim ~~29~~26, wherein the migraine is selected from the group consisting of: migraine without aura, migraine with aura, FHM1, FHM2, FHM4 and SHM.

~~31. The method of claim 29, wherein the migraine is migraine with aura.~~

~~32. The method of claim 29, wherein the migraine is FHM1.~~

~~33. The method of claim 29, wherein the migraine is FHM2.~~

~~34. The method of claim 29, wherein the migraine is FHM4.~~

~~35. The method of claim 29, wherein the migraine is SHM.~~

~~36~~28. The ~~method~~use of any one of claim~~s~~ ~~29~~26 or ~~35~~27, wherein the subject has an inadequate response to at least one medication used for the treatment of a migraine.

~~37~~29. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating or preventing cortical spreading depression (CSD) ~~in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~.

~~38~~30. Use of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, in the manufacture of a medicament for ~~A method of~~ treating or preventing a cranial neuropathy or multiple cranial neuropathies ~~in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13~~, wherein the cranial neuropathy is selected from the group consisting of bell palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy.

31. A compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, for use in therapy.