

ION CHANNEL MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application Number 62/677,903, filed May 30, 2018, and 62/738,508, filed September 28, 2018, each of which is incorporated herein by reference in its entirety.

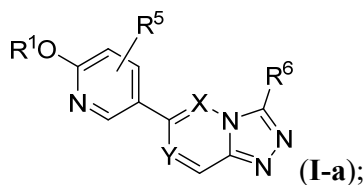
BACKGROUND

[0002] 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 (I_{NaL}) is a sustained component of the fast Na⁺ current of cardiac myocytes and neurons. Many common neurological and cardiac conditions are associated with abnormal I_{NaL} 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 I_{NaL}, are useful in treating such disease states.

SUMMARY

[0003] 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 sodium current (I_{NaL}). In one example, the present disclosure features compounds of Formula (I):

[0003a] In one aspect of the present disclosure, there is provided a compound represented by Formula I-a:



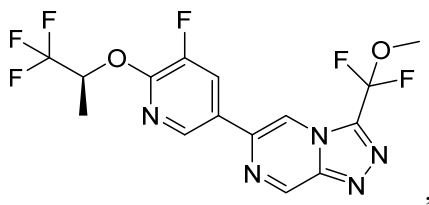
or a pharmaceutically acceptable salt thereof, wherein

X is CR^d and Y is N;

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R² is
R³ is
R⁴ is
R⁵ is
R⁶ is
R^a is
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- R^2 is C_{1-4} haloalkyl, phenyl, or monocyclic C_{3-6} cycloalkyl optionally substituted with one or more R^b ;
- R^3 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;
- R^4 is hydrogen or C_{1-4} alkyl;
- 5 R^5 is halo;
- R^6 is C_{1-4} alkyl or C_{1-4} haloalkyl, wherein said C_{1-4} alkyl or C_{1-4} haloalkyl are each substituted with OR^c ;
- R^a and R^b are each independently selected from is selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,
- 10 R^c is C_{1-4} alkyl optionally substituted with C_{3-6} cycloalkyl or C_{1-4} alkoxy, or C_{3-6} cycloalkyl; and
- R^d is hydrogen or C_{1-4} alkyl;
- or a pharmaceutically acceptable salt thereof.

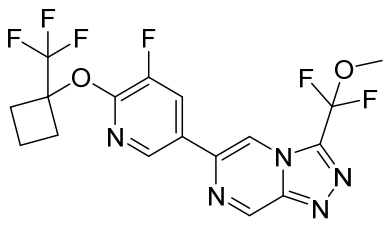
[0003b] In another aspect of the present disclosure, there is provided a crystalline compound of formula:



- 5 wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.7 ± 0.2 , 19.0 ± 0.2 , and 20.4 ± 0.2 , optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern

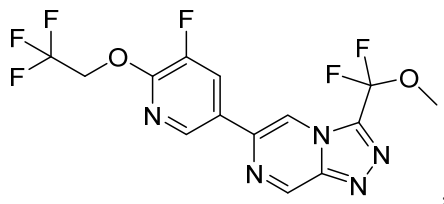
comprising peaks at the following diffraction angles (2θ): 7.2 ± 0.2 , 14.4 ± 0.2 , 16.7 ± 0.2 , 19.0 ± 0.2 , 20.4 ± 0.2 , and 25.7 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.2 ± 0.2 , 14.4 ± 0.2 , 16.7 ± 0.2 , 17.9 ± 0.2 , 19.0 ± 0.2 , 20.4 ± 0.2 , 20.8 ± 0.2 , 23.2 ± 0.2 , 25.7 ± 0.2 , and 28.0 ± 0.2 ,
5 optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 3A.

[0003c] In a further aspect of the present disclosure, there is provided a crystalline compound of formula:



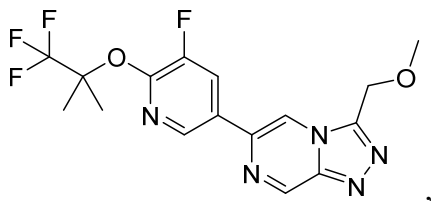
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 19.7 ± 0.2 , and 21.0 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 14.5 ± 0.2 , 15.3 ± 0.2 , 19.7 ± 0.2 , 21.0 ± 0.2 , and 24.2 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 11.6 ± 0.2 , 12.0 ± 0.2 , 14.5 ± 0.2 , 15.3 ± 0.2 , 19.1 ± 0.2 , 19.7 ± 0.2 , 21.0 ± 0.2 , 22.4 ± 0.2 , and 24.2 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 6A.

[0003d] In another aspect of the present disclosure, there is provided a crystalline compound of formula:



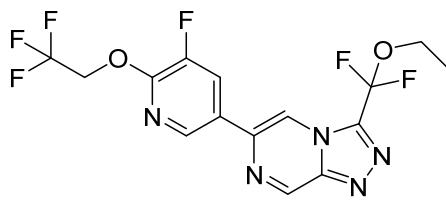
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 16.6 ± 0.2 , and 18.4 ± 0.2 , wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 13.8 ± 0.2 , 16.6 ± 0.2 , 18.4 ± 0.2 , 20.3 ± 0.2 , and 24.3 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 10.8 ± 0.2 , 13.8 ± 0.2 , 16.6 ± 0.2 , 17.8 ± 0.2 , 18.4 ± 0.2 , 19.5 ± 0.2 , 20.3 ± 0.2 , 21.2 ± 0.2 , and 24.3 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 7A.

[0003e] In another aspect of the present disclosure, there is provided a crystalline compound of formula:



wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.9 ± 0.2 , 19.8 ± 0.2 , and 23.7 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.9 ± 0.2 , 12.3 ± 0.2 , 14.1 ± 0.2 , 19.8 ± 0.2 , 20.7 ± 0.2 , and 23.7 ± 0.2 ; optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 9.9 ± 0.2 , 12.3 ± 0.2 , 14.1 ± 0.2 , 16.5 ± 0.2 , 17.2 ± 0.2 , 19.8 ± 0.2 , 20.7 ± 0.2 , 23.7 ± 0.2 , 24.8 ± 0.2 , 27.7 ± 0.2 , and 29.1 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 9A.

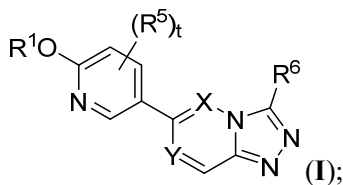
[0003f] In a further aspect of the present disclosure, there is provided a crystalline compound of formula:



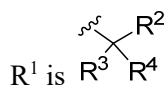
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2 θ): 9.3 $\pm$ 0.2, 18.8 $\pm$ 0.2, and 21.4 $\pm$ 0.2.

[0003h] 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 composition disclosed herein, in the manufacture of a medicament for treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof.

[0003j] 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 composition disclosed herein, in the manufacture of a medicament for treating a pain in a subject in need thereof.



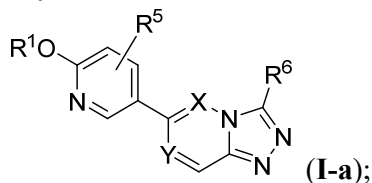
or a pharmaceutically acceptable salt thereof, wherein



25 R² is C₁₋₄haloalkyl, phenyl, or monocyclic C₃₋₆ cycloalkyl optionally substituted with one or more R^b;

Listing of Claims:

1. A compound represented by Formula **I-a**:



or a pharmaceutically acceptable salt thereof, wherein

X is CR^d and Y is N;



R¹ is R³, R⁴, monocyclic C₃₋₆ cycloalkyl, or 4- to 7-membered monocyclic heterocyclyl, wherein said cycloalkyl and heterocyclyl are optionally substituted with one or more R^a;

R² is C₁₋₄haloalkyl, phenyl, or monocyclic C₃₋₆ cycloalkyl optionally substituted with one or more R^b;

R³ is hydrogen, C₁₋₄alkyl, or C₁₋₄haloalkyl;

R⁴ is hydrogen or C₁₋₄alkyl;

R⁵ is halo;

R⁶ is C₁₋₄alkyl or C₁₋₄haloalkyl, wherein said C₁₋₄alkyl or C₁₋₄haloalkyl are each substituted with OR^c;

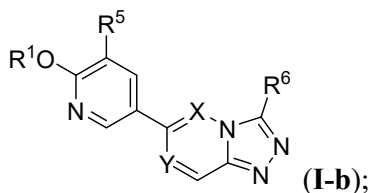
R^a and R^b are each independently selected from is selected from halo, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, and C₁₋₄haloalkoxy,

R^c is C₁₋₄alkyl optionally substituted with C₃₋₆ cycloalkyl or C₁₋₄alkoxy, or C₃₋₆ cycloalkyl; and

R^d is hydrogen or C₁₋₄alkyl;

or a pharmaceutically acceptable salt thereof.

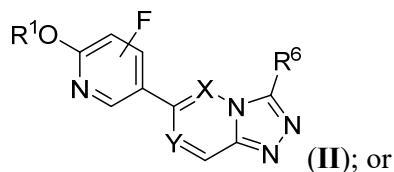
2. The compound of claim 1 represented by Formula **I-b**:



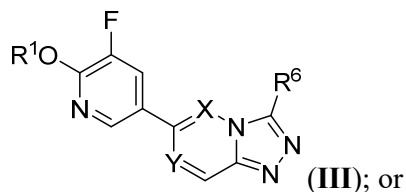
or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in claim 1.

3. The compound of claim 1, wherein the compound is represented by:

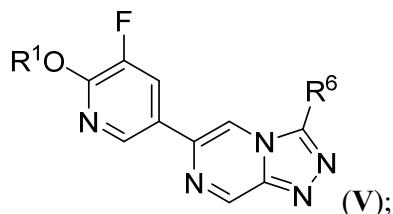
(a) Formula II:



(b) Formula III:



(c) Formula V:



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

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt

thereof, wherein R¹ is ; or R¹ is cyclobutyl optionally substituted with one or more R^a.

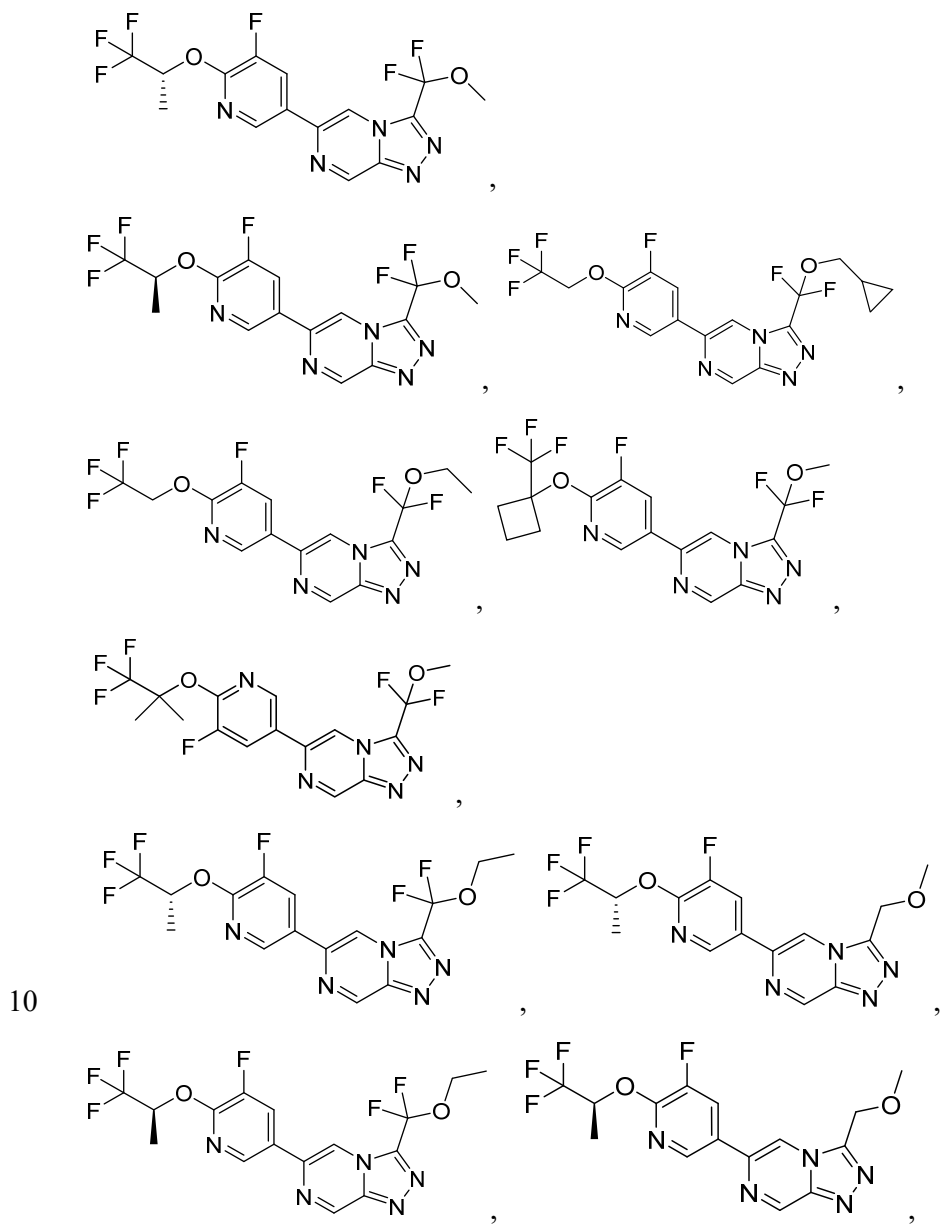
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R² is C₁₋₄haloalkyl, optionally wherein R² is CF₃.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein a) R³ is C₁₋₄alkyl and R⁴ is hydrogen or C₁₋₄alkyl; optionally wherein R³ and R⁴ are each C₁₋₄alkyl; or b) R³ and R⁴ are each hydrogen.

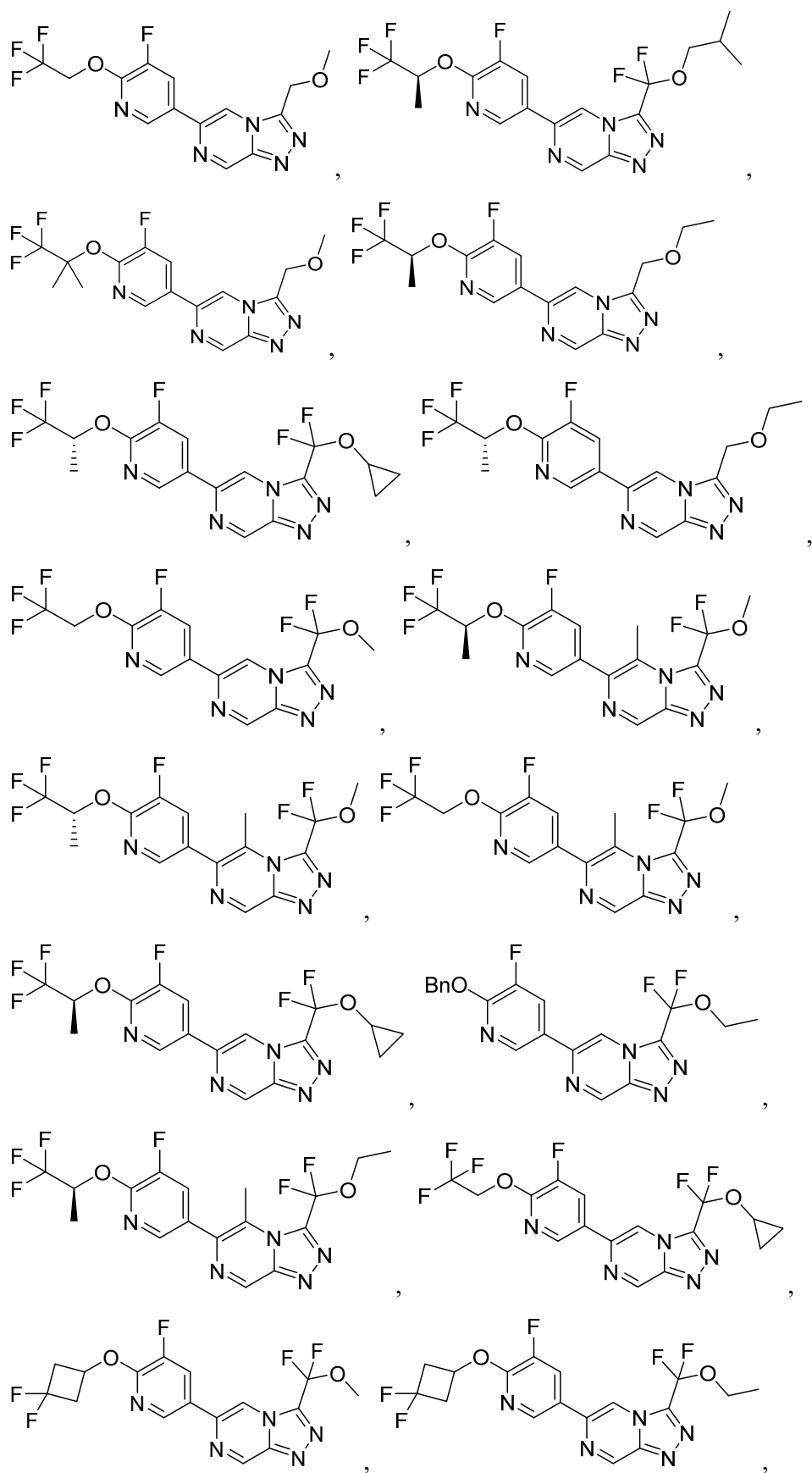
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -CF₂-OR^c, optionally wherein R^c is C₁₋₄alkyl optionally substituted with cyclopropyl or R^c is cyclopropyl.

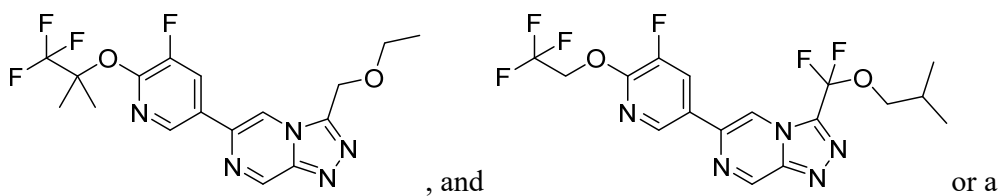
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-\text{CH}_2\text{-OR}^c$, optionally wherein R^c is C_{1-4} alkyl.

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



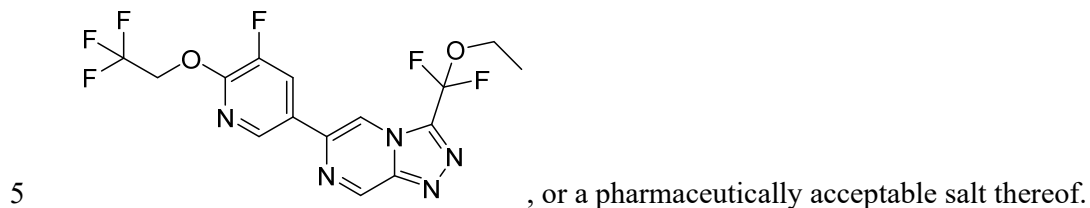
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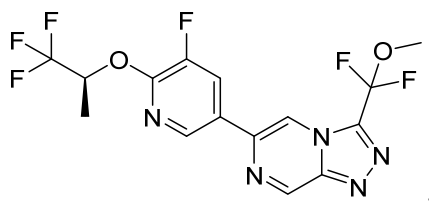


pharmaceutically acceptable salt thereof.

10. The compound of claim 9, wherein the compound is:

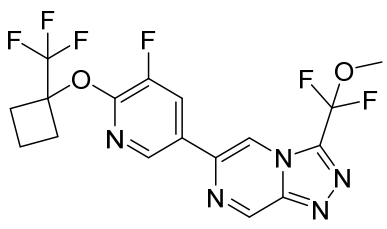


11. A crystalline compound of formula:



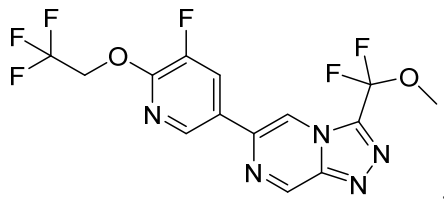
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.7 ± 0.2 , 19.0 ± 0.2 , and 20.4 ± 0.2 , optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.2 ± 0.2 , 14.4 ± 0.2 , 16.7 ± 0.2 , 19.0 ± 0.2 , 20.4 ± 0.2 , and 25.7 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.2 ± 0.2 , 14.4 ± 0.2 , 16.7 ± 0.2 , 17.9 ± 0.2 , 19.0 ± 0.2 , 20.4 ± 0.2 , 20.8 ± 0.2 , 23.2 ± 0.2 , 25.7 ± 0.2 , and 28.0 ± 0.2 , optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 3A.

12. A crystalline compound of formula:



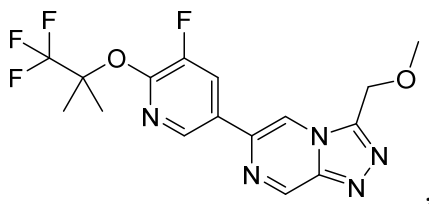
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 19.7 ± 0.2 , and 21.0 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 14.5 ± 0.2 , 15.3 ± 0.2 , 19.7 ± 0.2 , 21.0 ± 0.2 , and 24.2 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 5.8 ± 0.2 , 11.6 ± 0.2 , 12.0 ± 0.2 , 14.5 ± 0.2 , 15.3 ± 0.2 , 19.1 ± 0.2 , 19.7 ± 0.2 , 21.0 ± 0.2 , 22.4 ± 0.2 , and 24.2 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 6A.

13. A crystalline compound of formula:



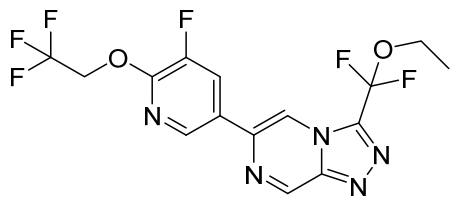
wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 16.6 ± 0.2 , and 18.4 ± 0.2 , wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 13.8 ± 0.2 , 16.6 ± 0.2 , 18.4 ± 0.2 , 20.3 ± 0.2 , and 24.3 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 10.8 ± 0.2 , 13.8 ± 0.2 , 16.6 ± 0.2 , 17.8 ± 0.2 , 18.4 ± 0.2 , 19.5 ± 0.2 , 20.3 ± 0.2 , 21.2 ± 0.2 , and 24.3 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 7A.

14. A crystalline compound of formula:



wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.9 ± 0.2 , 19.8 ± 0.2 , and 23.7 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.9 ± 0.2 , 12.3 ± 0.2 , 14.1 ± 0.2 , 19.8 ± 0.2 , 20.7 ± 0.2 , and 23.7 ± 0.2 ; optionally, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.3 ± 0.2 , 9.9 ± 0.2 , 12.3 ± 0.2 , 14.1 ± 0.2 , 16.5 ± 0.2 , 17.2 ± 0.2 , 19.8 ± 0.2 , 20.7 ± 0.2 , 23.7 ± 0.2 , 24.8 ± 0.2 , 27.7 ± 0.2 , and 29.1 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 9A.

15. A crystalline compound of formula:



wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.3 ± 0.2 , 18.8 ± 0.2 , and 21.4 ± 0.2 .

16. The crystalline compound of claim 15, wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.3 ± 0.2 , 16.1 ± 0.2 , 18.8 ± 0.2 , 21.1 ± 0.2 , 21.4 ± 0.2 , and 21.6 ± 0.2 , optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 9.3 ± 0.2 , 16.1 ± 0.2 , 18.8 ± 0.2 , 21.1 ± 0.2 , 21.4 ± 0.2 , 21.6 ± 0.2 , 22.6 ± 0.2 , 23.9 ± 0.2 , 26.0 ± 0.2 , and 26.4 ± 0.2 ; optionally wherein the crystalline compound is characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 1A.

17. A composition comprising a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.
- 5 18. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, or a composition of claim 17, in the manufacture of a medicament for treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof.
19. The use of claim 18, wherein the condition is a neurological or psychiatric disorder.
- 10 20. The use of claim 18 or 19, wherein the condition is epilepsy or an epilepsy syndrome, optionally wherein the condition is a genetic epilepsy, a genetic epilepsy syndrome, a pediatric epilepsy, or a pediatric epilepsy syndrome.
- 15 21. The use of any one of claims 18-20, wherein the condition is epileptic encephalopathy, optionally wherein the epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome.
- 20 22. The use of claim 18 or 19, 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,
- 25 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.
- 30 23. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, or a composition of claim 17, in the manufacture of a medicament for treating a neurological disorder or a psychiatric disorder in a subject in need thereof.

24. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, or a composition of claim 17, in the manufacture of a medicament for treating a pain in a subject in need thereof.