

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.

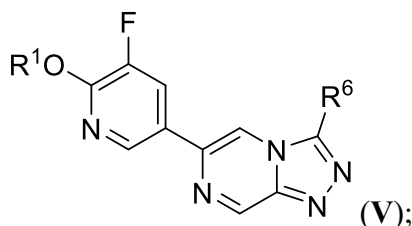
BACKGROUND

[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 V:



or a pharmaceutically acceptable salt thereof, wherein



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;

5 R⁶ is CF₂-OR^c;

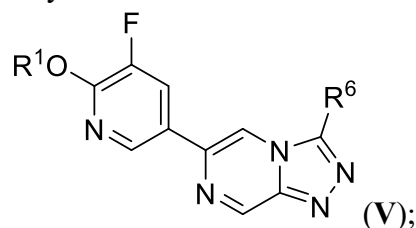
R^a and R^b are each independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, and C₁₋₄haloalkoxy, and

R^c is C₁₋₄alkyl optionally substituted with cyclopropyl, or wherein R^c is cyclopropyl; or a pharmaceutically acceptable salt thereof.

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Listing of Claims:

1. A compound represented by Formula V:



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or a pharmaceutically acceptable salt thereof, wherein

 R¹ is  , 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;

- 10 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;

R⁶ is CF₂-OR^c;

- 15 R^a and R^b are each independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, and C₁₋₄haloalkoxy, and

R^c is C₁₋₄alkyl optionally substituted with cyclopropyl, or wherein R^c is cyclopropyl; or a pharmaceutically acceptable salt thereof.

- 20 2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is

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

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² is C₁₋₄haloalkyl, optionally wherein R² is CF₃.

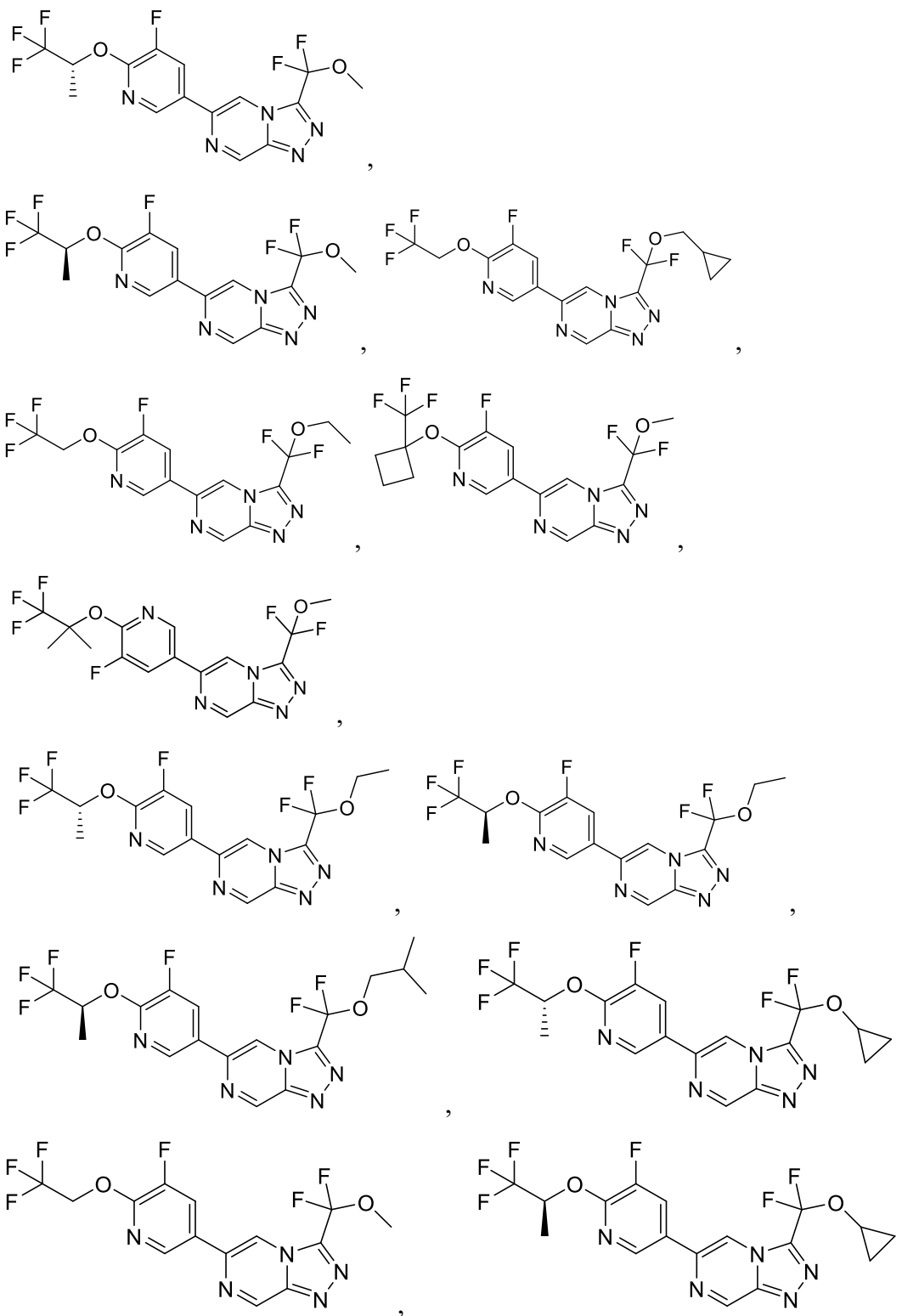
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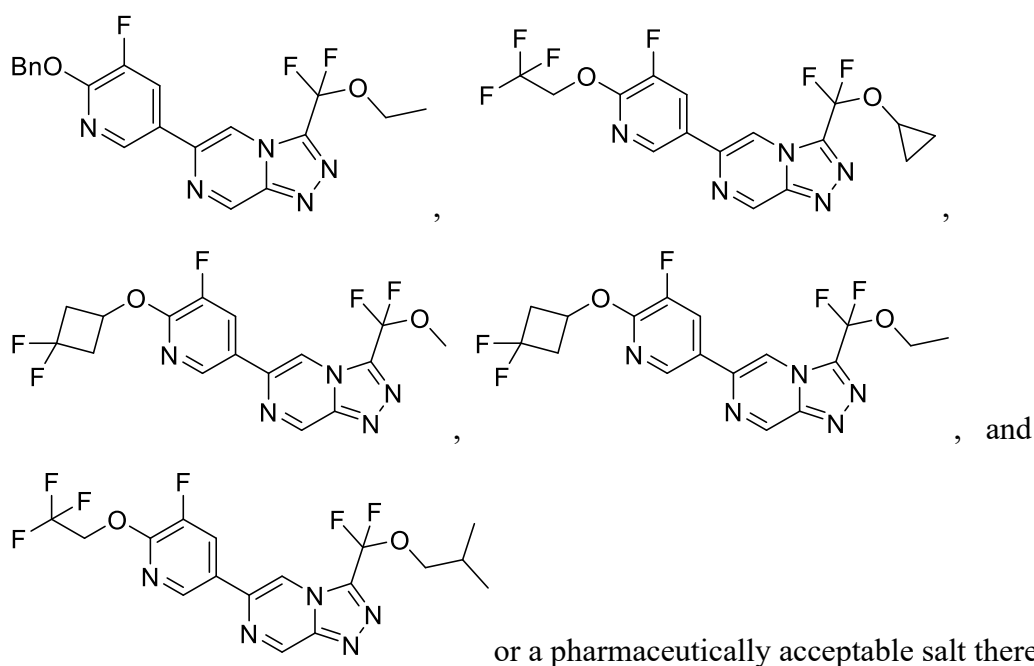
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein a) R³ is C₁₋₄alkyl and R⁴ is hydrogen or C₁₋₄alkyl; optionally wherein R³ and R⁴ are each C₁₋₄alkyl; or b) R³ and R⁴ are each hydrogen.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^c is C₁₋₄ alkyl.

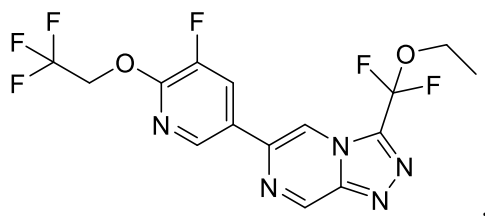
6. The compound of claim 1, wherein the compound is selected from the group

5 consisting of:



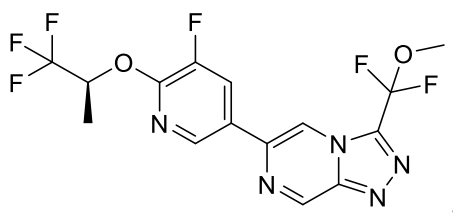


- 5 7. The compound of claim 6, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

8. A crystalline compound of formula:



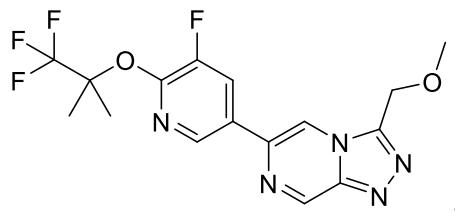
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wherein the crystalline compound is characterized by an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.7 ± 0.2 , 19.0 ± 0.2 , and 20.4 ± 0.2 , optionally, wherein the crystalline compound is characterized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

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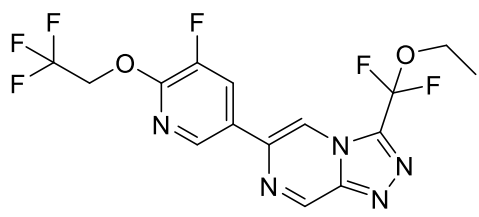
characterized by an X-ray powder diffraction pattern substantially the same as depicted in FIG. 7A.

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): 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.

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): 9.3 ± 0.2 , 18.8 ± 0.2 , and 21.4 ± 0.2 .

13. The crystalline compound of claim 12, 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.

- 5 14. A composition comprising a compound of any one of claims 1-13, or a
pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.
15. Use of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt
thereof, or a composition of claim 14, in the manufacture of a medicament for treating a
10 condition relating to aberrant function of a sodium ion channel in a subject in need thereof.
16. The use of claim 15, wherein the condition is a neurological or psychiatric disorder.
17. The use of claim 15 or 16, wherein the condition is epilepsy or an epilepsy syndrome,
15 optionally wherein the condition is a genetic epilepsy, a genetic epilepsy syndrome, a
pediatric epilepsy, or a pediatric epilepsy syndrome.
18. The use of any one of claims 15-17, wherein the condition is epileptic
encephalopathy, optionally wherein the epileptic encephalopathy is selected from the group
20 consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome.
19. The use of claim 15 or 16, wherein the condition is selected from the group consisting
of epileptic encephalopathy, epileptic encephalopathy with SCN1A mutation, epileptic
encephalopathy with SCN2A, epileptic encephalopathy with SCN8A mutation, early infantile
25 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, focal
epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation,
sudden unexpected death in epilepsy (SUDEP), Rasmussen encephalitis, malignant migrating
30 partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, KCNQ2
epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

20. Use of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, or a composition of claim 14, in the manufacture of a medicament for treating a neurological disorder or a psychiatric disorder in a subject in need thereof.

5 21. Use of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, or a composition of claim 14, in the manufacture of a medicament for treating a pain in a subject in need thereof.

22. The use of any one of claims 15-21, wherein the subject is a human.

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