FORMULATIONS OF ION CHANNEL MODULATORS AND METHODS OF PREPARATION AND USE OF ION CHANNEL MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 62/941,322, filed November 27, 2019; U.S. Provisional Patent Application No. 62/941,319, filed November 27, 2019; U.S. Provisional Patent Application No. 63/001,906, filed March 30, 2020; U.S. Provisional Patent Application No. 63/001,801, filed March 30, 2020; U.S. Provisional Patent Application No. 63/028,229, filed May 21, 2020; U.S. Provisional Patent Application No. 63/082,864, filed September 24, 2020; and U.S. Provisional Patent Application No. 63/082,857, filed September 24, 2020, the entire contents of each 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 compositions or dosage forms comprising 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 composition comprising:

from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg, from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, or about 50 mg) of Compound 1; and

a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a composition comprising:

a plurality of particles of Compound 1; and

a pharmaceutically acceptable excipient,

wherein the amount of the plurality of particles of Compound 1 in the composition is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg, from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, or about 50 mg).

In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein or use of a composition comprising from about 2.5 mg to about 90 mg of Compound 1 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.

In another aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating a neurological disorder, a psychiatric disorder, pain or cancer in a subject in need thereof.

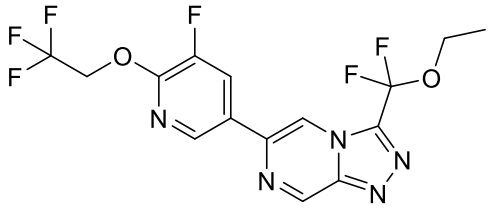
In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein or use of a therapeutically effective amount of Compound 1, e.g., from 2.5 mg to 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of the composition disclosed herein or use of a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a migraine in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein or use of a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing cortical spreading depression (CSD) in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of the composition disclosed herein or use of an effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof.

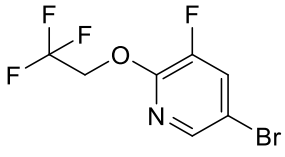
In a further aspect of the present disclosure, there is provided a method of making Compound 1:



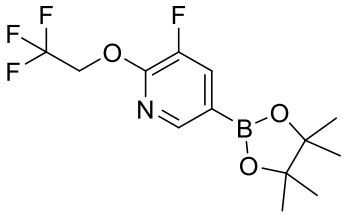
,

or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

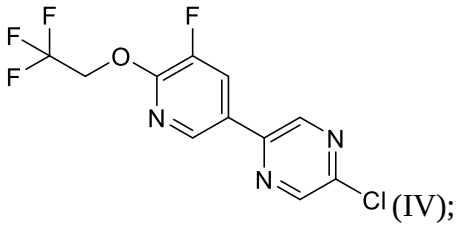
(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):


(II);

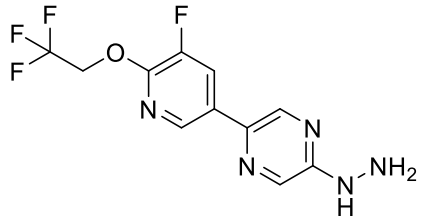
(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):


(III);

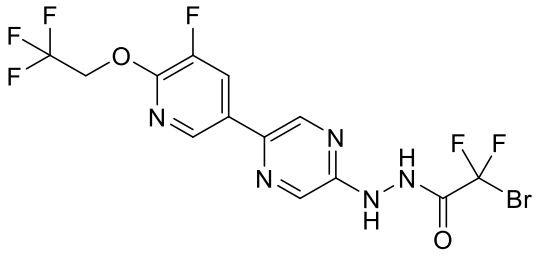
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

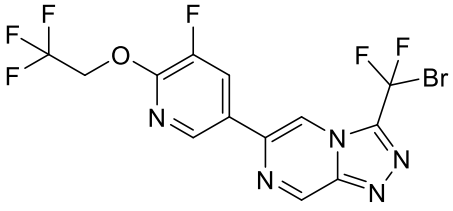
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):

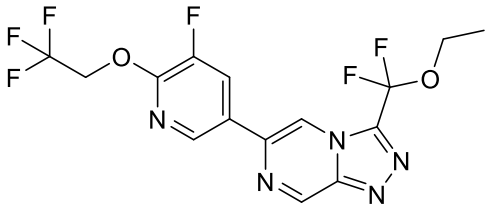

(VI);

(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):

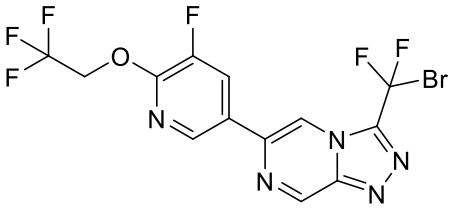

(VII); and

(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a method of making Compound 1:


(I)

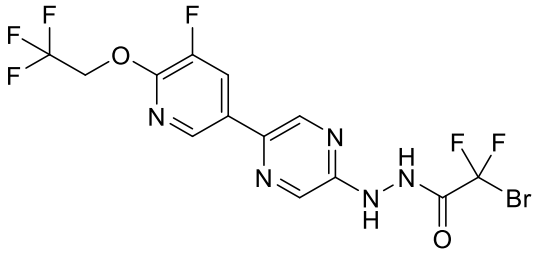
or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):



(VII)

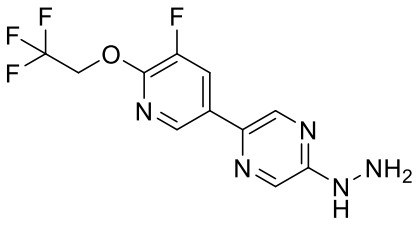
with a silver catalyst and ethanol; optionally:

wherein the compound of formula (VII) is provided by contacting the compound of formula (VI):



(VI)

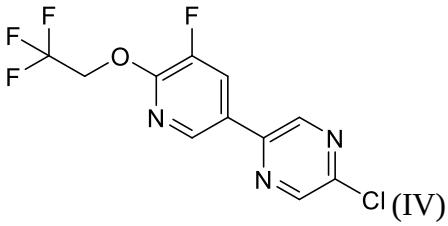
with an acid; further optionally wherein the compound of formula (VI) is provided by contacting the compound of formula (V):



(V)

with 2-bromo-2,2-difluoro-acetyl chloride; further optionally

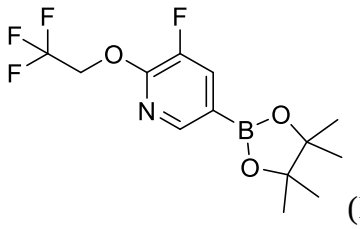
wherein the compound of formula (V) is provided by contacting the compound of formula (IV):



(IV)

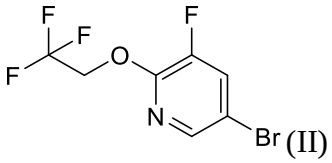
with hydrazine; further optionally

wherein the compound of formula (IV) is provided by contacting the compound of formula (III):



(III)

with a palladium catalyst and 2-bromo-5-chloro-pyrazine; further optionally wherein the compound of formula (III) is provided by contacting the compound of formula (II):



(II)

with a palladium catalyst and bis(pinacolato)diboron.

In a further aspect of the present disclosure, there is provided a composition disclosed herein, or a composition comprising from about 2.5 mg to about 90 mg of Compound 1, for use in therapy.

Described herein are compositions or dosage forms 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 (INaL). The present disclosure also comprises methods for modulating the sodium channel activity using a compound, composition, or dosage form described herein. Also provided herein is a method of preparing ion channel modulators.

In one example, the present disclosure provides a dosage form comprising: from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and a pharmaceutically acceptable excipient.

In another example, the present disclosure provides a dosage form comprising: a plurality of particles of Compound 1; and a pharmaceutically acceptable excipient, wherein the amount of the plurality of particles of Compound 1 in the dosage form is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).

In one example, the present disclosure provides a composition in a dosage form comprising: from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and a pharmaceutically acceptable excipient.

In another example, the present disclosure provides a composition in a dosage form comprising: a plurality of particles of Compound 1; and a pharmaceutically acceptable excipient, wherein the amount of the plurality of particles of Compound 1 in the composition is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).In another 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 dosage form disclosed herein. Also 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 from about 2.5 mg to about 90 mg of Compound 1. In some examples, the condition is a neurological or psychiatric disorder In some examples, the condition is epilepsy or an epilepsy syndrome. In some examples, the condition is a genetic epilepsy or a genetic epilepsy syndrome. In some examples, the condition is a pediatric epilepsy or a pediatric epilepsy syndrome. In some examples, the condition is epileptic encephalopathy. In some examples, the condition is developmental. In some examples, the epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome. In other 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 some examples, the condition is a cancer.

Also provided herein is a method of treating a neurological disorder or a psychiatric disorder in a subject in need thereof, wherein the method comprises administering to a subject in need thereof a dosage form disclosed herein.

The disclosure provides, in part, a method of treating a pain in a subject in need thereof, wherein the method comprises administering to the subject a dosage form disclosed herein.

Contemplated methods include a method of treating a cancer in a subject in need thereof, wherein the method comprises administering to the subject a dosage form disclosed herein.

In another example, provided herein is 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 dosage form disclosed herein.

Also provided herein is 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 Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

In another 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 dosage form disclosed herein.

Provided herein, in part, 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 Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

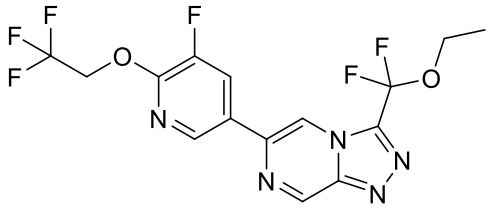
In another example, a method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form disclosed herein is provided.

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 Compound 1, e.g., from about 2.5 mg to about 90 mg is also provided.

Also provided herein is 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 dosage form described herein.

In another example, 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 Compound 1, e.g., from 2.5 mg to about 90 mg of Compound 1.

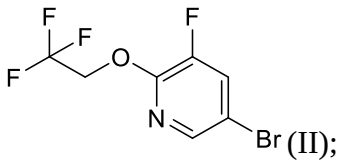
In another example, the present disclosure provides a method of making Compound 1:



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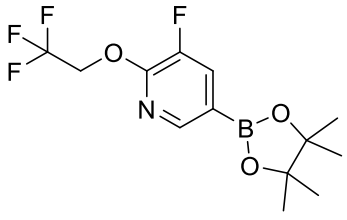
or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):



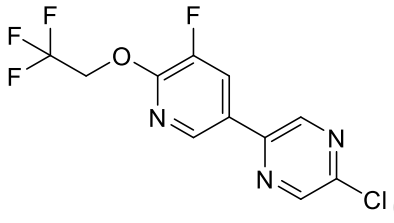
(II);

(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):



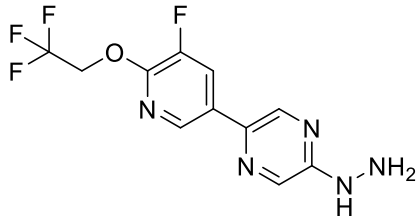
(III);

(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):

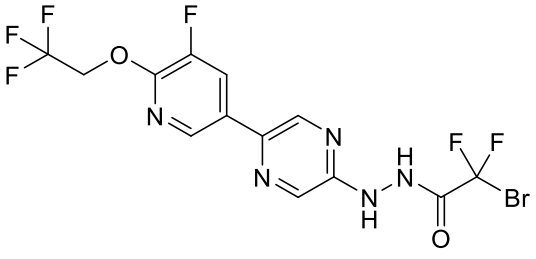


(IV);

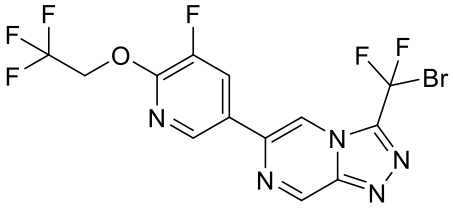
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):

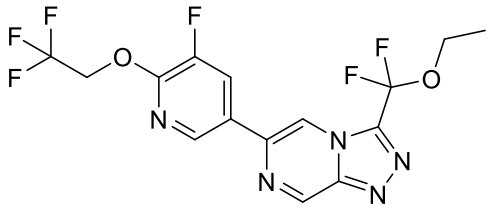

(VI);

(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):


(VII); and

(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

In another example, the present disclosure provides a method of making Compound 1:


,

or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):

Claims

1. A composition comprising:

from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg, from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, or about 50 mg) of Compound 1; and

a pharmaceutically acceptable excipient.

2. A composition comprising:

a plurality of particles of Compound 1; and

a pharmaceutically acceptable excipient,

wherein the amount of the plurality of particles of Compound 1 in the composition is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg, from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, or about 50 mg).

3. The composition of claim 1 or 2, wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm; or wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm; or wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 2 μm; or wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm (e.g., less than about 15 μM); or wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 5 μm; or wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm, 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm and 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm.

4. The composition of any one of claims 1-3, wherein the composition is for oral administration; optionally wherein the composition is in a solid form.

5. The composition of any one of claims 1-4, wherein Compound 1 is in a crystalline form.

6. The composition of claim 5, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 12.6±0.2, 15.8±0.2, and 18.6±0.2; or wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 15.8±0.2, 18.6±0.2, and 22.6±0.2; or wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 14.9±0.2, 15.8±0.2, 16.6±0.2, 16.8±0.2, 18.6±0.2, 21.0±0.2 and 22.6±0.2; orwherein the crystalline form exhibits an X-ray powder diffraction pattern substantially the same as depicted in FIG. 1.

7. The composition of any one of claims 1-6, wherein the composition is in the form of a capsule or a blend.

8. The composition of claim 7, wherein the pharmaceutical excipient is a filler (e.g., microcrystalline cellulose or starch) or a lubricant; optionally wherein the ratio of Compound 1 to the filler is about 1:1 or about 1:10.

9. The composition of claim 7 or 8, wherein the pharmaceutical excipient is a filler.

10. The composition of any one of claims 7-9, wherein the composition comprises:

from about 50% to 90% by weight filler and

from 0% to about 5% by weight lubricant; or

from about 1% to about 50% by weight Compound 1;

from about 50% to about 90% by weight filler; and

from 0% to about 4% by weight lubricant.

11. The composition of any one of claims 1, 2, or 4, wherein the composition is in a liquid form.

12. The composition of claim 11, wherein the composition is in the form of a solution.

13. The composition of claim 12, wherein the pharmaceutical excipient is selected from the group consisting of a co-solubilizer/co-solvent (e.g., polymer (e.g., PEG 400)), an emulsifier (e.g., a castor oil derivative, e.g., Kolliphor RH40), a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), a vitamin derivative (e.g., Vitamin ETPGS)), a solvent (e.g., propylene glycol, ethanol, diethylene glycol monoethyl ether (or Transcutol HP)).

14. The composition of any one of claims 11-13, wherein the concentration of Compound 1 is from about 0.1 mg/mL to about 10 mg/mL.

15. The composition of any one of claims 11-13, wherein the composition comprises:

from about 35% to about 45% by weight a filler (e.g., a polymer (e.g., PEG 400));

from about 5% to about 15% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is about 0.5 mg/mL or about 0.25 mg/mL; or

wherein the composition comprises:

from about 55% to about 60% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 15% to about 20% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS);

from about 5% to about 10% by weight propylene glycol; and

from about 15% to about 20% by weight ethanol;

wherein the concentration of Compound 1 is from about 5 mg/mL to about 10 mg/mL, or from about 2.5 mg/mL to about 5 mg/mL; or

wherein the composition comprises:

from about 65% to about 70% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 18% to about 23% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS); and

from about 7% to about 12% by weight propylene glycol;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 10 mg/mL or from about 0.5 mg/mL to about 5 mg/mL; or

wherein the composition comprises:

from about 35% to about 45% by weight diethylene glycol monoethyl ether (Transcutol HP);

from about 5% to about 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin derivative (e.g., Vitamin ETPGS)); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 5 mg/mL or from about 0.5 mg/mL to about 2.5 mg/mL; or

wherein the composition comprises:

from about 30% to about 40% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 40% to about 50% by weight a surfactant (e.g., a glyceride (e.g., Capmul MCM C8);

from about 5% to 15% by weight a plasticizer (e.g., triethyl citrate); and

from about 5% to about 15% by weight a solvent (e.g., ethanol); or

wherein the composition comprises:

from about 35% to about 45% by weight a propylene glycol monocaprylate (e.g., Capryol 90);

from about 15% to about 25% by weight a glyceride (e.g., caprylocaproyl macrogolglycerides (e.g., Labrasol)) and

from about 35% to 45% by weight diethylene glycol monoethyl ether (e.g., Transcutol HP).

16. The composition of any one of claims 1, 2, 4, and 11, wherein the composition is in the form of a suspension; optionally wherein the concentration of Compound 1 is about 0.1 mg/mL, about 0.5 mg, about 1 mg/mL, about 5 mg/mL, about 10 mg/mL, or about 15 mg/mL of Compound 1.

17. The composition of claim 16, wherein the pharmaceutical excipient comprises:

about 0.5% by weight a filler (e.g., methylcellulose, e.g., 400 cP MC); and

about 0.2% by weight an emulsifier (e.g., Tween 80, e.g., Poloxamer 188); optionally wherein the pharmaceutical excipient further comprises about 1% by weight a preservative solution (e.g., paraben solution).

18. The composition of any one of claims 1, 2, and 4, wherein Compound 1 is amorphous.

19. The composition of any one of claims 1, 2, 4, and18, wherein the composition is in the form of amorphous solid dispersion.

20. The composition of claim 19, wherein the pharmaceutical excipient is a polymer (e.g., soluplus, Eudragit, and HPMC ASMF).

21. The composition of any one of claims 1-20, wherein the composition is stable (e.g., chemically stable) at 25°C and 60% RH for 7 days, 14 days, 21 days, 28 days, 1 month, 3 months, or 6 months.

22. Use of the composition of any one of claims 1-21 or use of a composition comprising from about 2.5 mg to about 90 mg of Compound 1 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.

23. The use of claim 22, wherein the condition is a neurological or psychiatric disorder, optionally wherein the condition is epilepsy or an epilepsy syndrome; further optionally wherein the condition is a genetic epilepsy, a genetic epilepsy syndrome, a pediatric epilepsy or a pediatric epilepsy syndrome.

24. The use of claim 22, wherein the condition is developmental or epileptic encephalopathy, optionally wherein the developmental or epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome, further optionally wherein the condition is selected from the group consisting of epileptic encephalopathy, developmental and 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.

25. The use of claim 22, wherein the condition is a cancer.

26. Use of the composition of any one of claims 1-21 in the manufacture of a medicament for treating a neurological disorder, a psychiatric disorder, pain or cancer in a subject in need thereof.

27. Use of the composition of any one of claims 1-21 or use of a therapeutically effective amount of Compound 1, e.g., from 2.5 mg to 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof.

28. The use of claim 27, 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; optionally: wherein the TAC is a short-lasting unilateral neuralgiform headache attack; or wherein the TAC is SUNCT; or wherein the TAC is SUNA; further optionally wherein the subject has an inadequate response to at least one medication used for the treatment of a TAC.

29. Use of the composition of any one of claims 1-21 or use of a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a migraine in a subject in need thereof.

30. The use of claim 28, 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), optionally: wherein the migraine is migraine without aura, or wherein the migraine is migraine with aura; or wherein the migraine is FHM1; or wherein the migraine is FHM2; or wherein the migraine is FHM4; or wherein the migraine is SHM; further optionally wherein the subject has an inadequate response to at least one medication used for the treatment of a migraine.

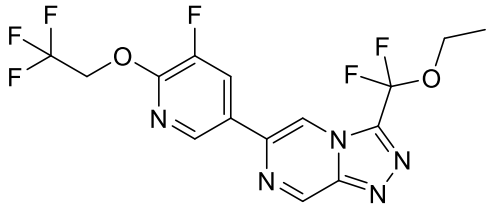
31. Use of the composition of any one of claim 1-21 or use of a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing cortical spreading depression (CSD) in a subject in need thereof.

32. Use of the composition of any one of claims 1-21 or use of an effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1 in the manufacture of a medicament for treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof.

33. The use of claim 32, 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.

34. The use of any one of claims 22-33, wherein the composition is administered orally; optionally wherein the composition is a capsule; further optionally wherein the subject is 18 to 65 years of age.

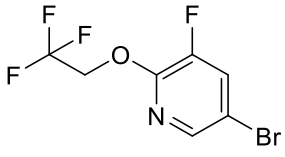
35. A method of making Compound 1:



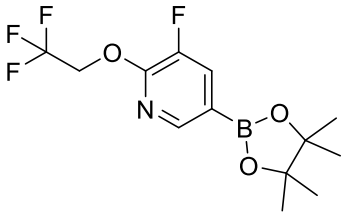
,

or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

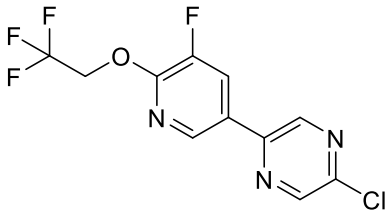
(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):


(II);

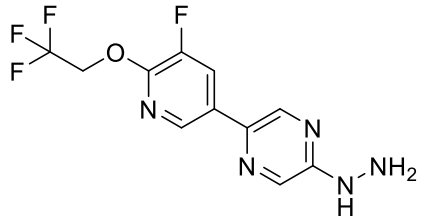
(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):


(III);

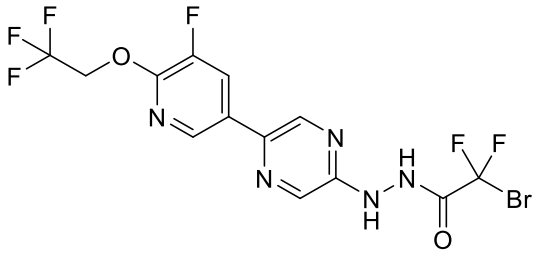
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

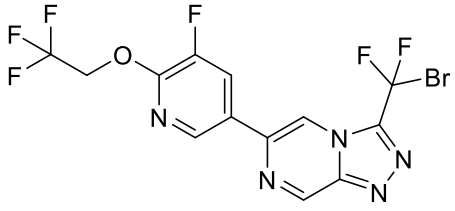
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):


(VI);

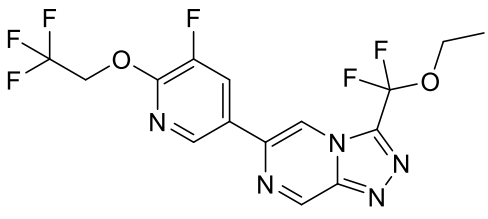
(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):


(VII); and

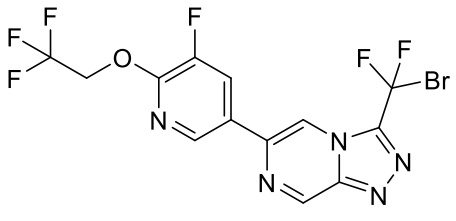
(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

36. The method of claim 35, wherein the palladium catalyst in step (ii) or (iii) is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride; and/or wherein the silver catalyst in step (vii) is silver tetrafluoroborate; and/or wherein the acid in step (vi) is *p*-toluenesulfonic acid.

37. A method of making Compound 1:

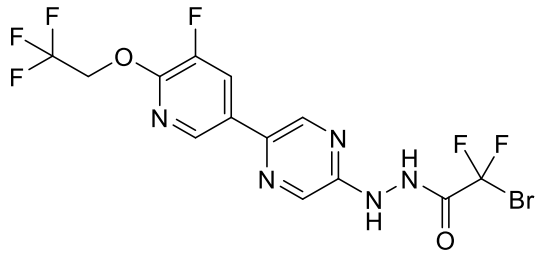

(I)

or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):

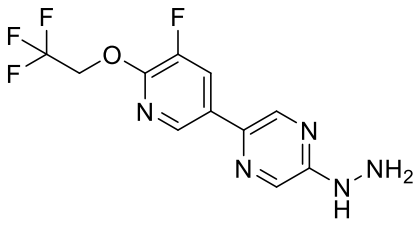

(VII)

with a silver catalyst and ethanol; optionally:

wherein the compound of formula (VII) is provided by contacting the compound of formula (VI):

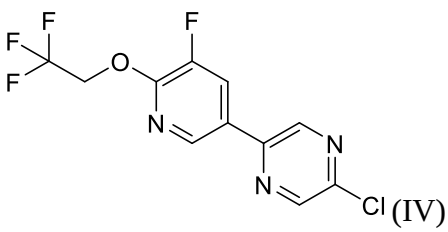

(VI)

with an acid; further optionally wherein the compound of formula (VI) is provided by contacting the compound of formula (V):


(V)

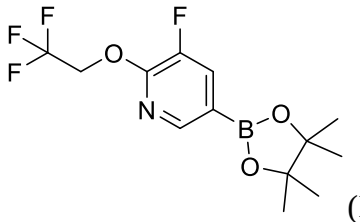
with 2-bromo-2,2-difluoro-acetyl chloride; further optionally

wherein the compound of formula (V) is provided by contacting the compound of formula (IV):

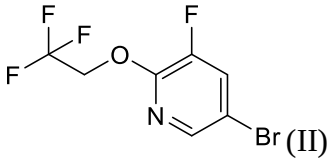

(IV)

with hydrazine; further optionally

wherein the compound of formula (IV) is provided by contacting the compound of formula (III):


(III)

with a palladium catalyst and 2-bromo-5-chloro-pyrazine; further optionally wherein the compound of formula (III) is provided by contacting the compound of formula (II):


(II)

with a palladium catalyst and bis(pinacolato)diboron.

38. The method of claim 37, wherein the compound of formula (II) is provided by contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine.

39. The method of any one of claims 35-38, wherein the silver catalyst is silver tetrafluoroborate; and/or wherein the acid is *p*-toluenesulfonic acid; and /or wherein the palladium catalyst is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

40. The composition of any one of claims 1-21, or a composition comprising from about 2.5 mg to about 90 mg of Compound 1, for use in therapy.