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.

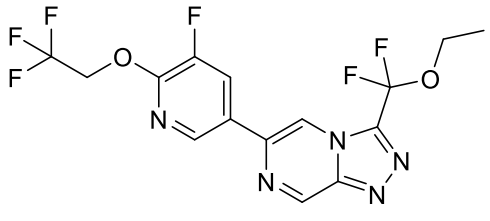
BACKGROUND

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



; and a pharmaceutically acceptable excipient:

wherein the composition is in the form of a capsule or a blend;

wherein the pharmaceutically acceptable excipient is a filler; and

wherein the pharmaceutical composition comprises:

from 50% to 90% by weight filler and

from 0% to 5% by weight lubricant; or

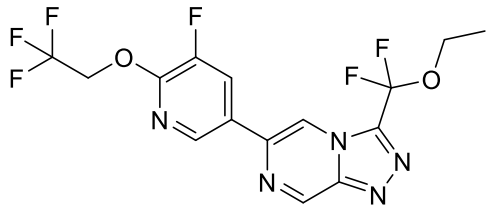
from 1% to 50% by weight Compound 1;

from 50% to 90% by weight filler; and

from 0% to 4% by weight lubricant.

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

wherein the composition is in the form of a capsule or a blend;

wherein the pharmaceutically acceptable excipient is a filler; and

wherein the pharmaceutical composition comprises:

from 50% to 90% by weight filler and

from 0% to 5% by weight lubricant; or

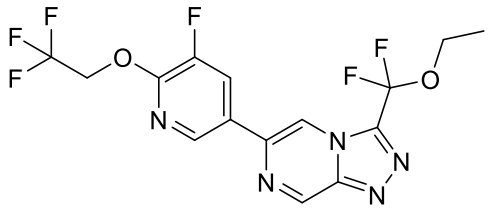
from 1% to 50% by weight Compound 1;

from 50% to 90% by weight filler; and

from 0% to 4% by weight lubricant.

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

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



; and

a pharmaceutically acceptable excipient;

wherein the composition is in a liquid form;

wherein the composition comprises:

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

from 5% to 15% by weight an emulsifier (e.g., Kolliphor RH40); and

from 40% to 60% by weight water;

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

wherein the composition comprises:

from 55% to 60% by weight an emulsifier (e.g., Kolliphor RH40);

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

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

from 15% to 20% by weight ethanol;

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

wherein the composition comprises:

from 65% to 70% by weight an emulsifier (e.g., Kolliphor RH40);

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

from 7% to 12% by weight propylene glycol;

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

wherein the composition comprises:

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

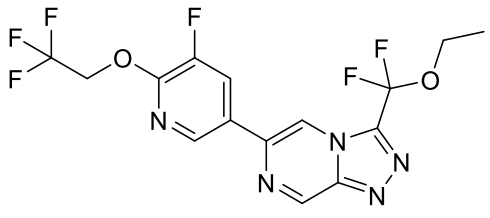
from 5% to 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin (e.g., Vitamin ETPGS)); and

from 40% to 60% by weight water;

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

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

wherein the composition is in a liquid form;

wherein the composition comprises:

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

from 5% to 15% by weight an emulsifier (e.g., Kolliphor RH40); and

from 40% to 60% by weight water;

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

wherein the composition comprises:

from 55% to 60% by weight an emulsifier (e.g., Kolliphor RH40);

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

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

from 15% to 20% by weight ethanol;

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

wherein the composition comprises:

from 65% to 70% by weight an emulsifier (e.g., Kolliphor RH40);

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

from 7% to 12% by weight propylene glycol;

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

wherein the composition comprises:

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

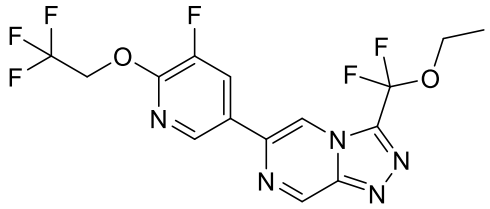
from 5% to 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin (e.g., Vitamin ETPGS)); and

from 40% to 60% by weight water;

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

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

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



; and a pharmaceutically acceptable excipient;

wherein the composition is in the form of a suspension; optionally wherein the concentration of Compound 1 is 0.1 mg/mL, 0.5 mg, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 15 mg/mL of Compound 1; and

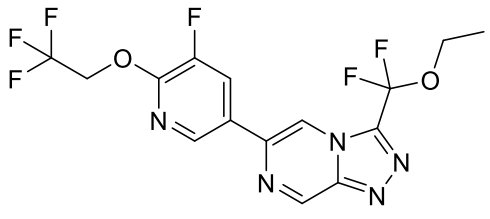
wherein the pharmaceutically acceptable excipient comprises:

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

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

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

wherein the composition is in the form of a suspension; optionally wherein the concentration of Compound 1 is 0.1 mg/mL, 0.5 mg, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 15 mg/mL of Compound 1; and

wherein the pharmaceutically acceptable excipient comprises:

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

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

In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating a condition wherein the condition is a neurological or psychiatric disorder.

In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating cancer.

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 in the manufacture of a medicament for treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof.

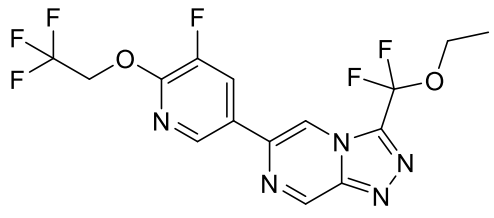
In another aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating or preventing a migraine in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein 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 in the manufacture of a medicament for treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof.

In another aspect of the present disclosure, there is provided the composition as disclosed herein for use in therapy.

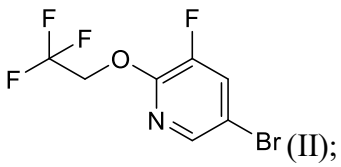
In a further aspect of the present disclosure, there is provided a method of making Compound 1:



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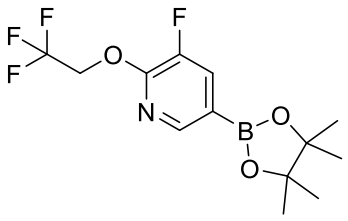
or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

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

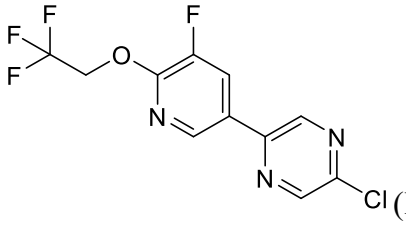


(II);

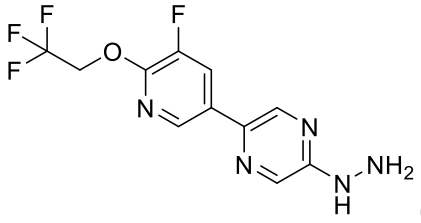
(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):


(III);

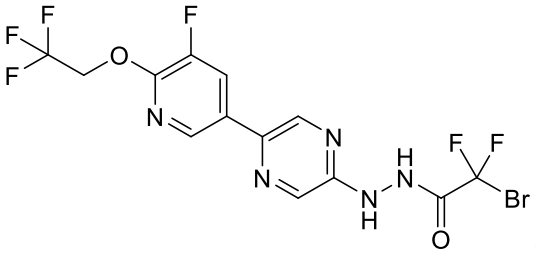
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

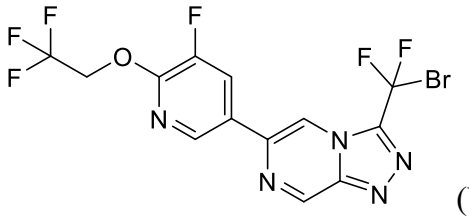
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

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

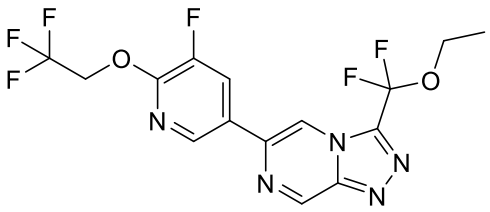

(VI);

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

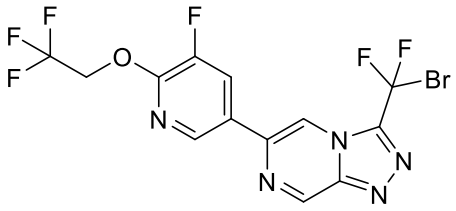

(VII); and

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

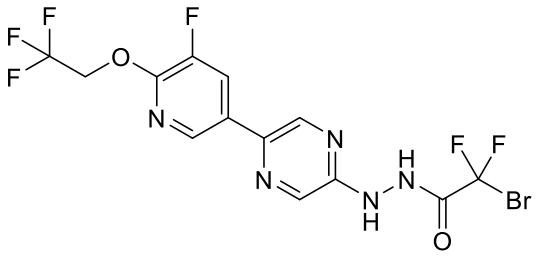

(I)

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)

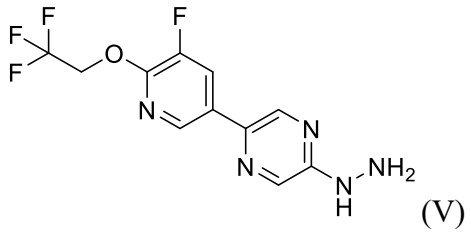
with a silver catalyst and ethanol;

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


(VI)

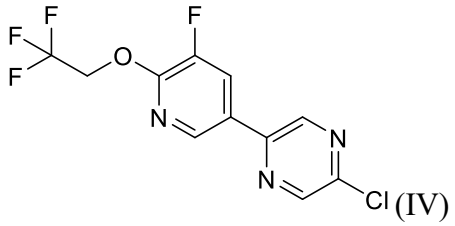
with an acid;

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


(V)

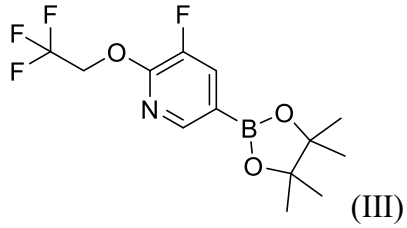
with 2-bromo-2,2-difluoro-acetyl chloride;

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


(IV)

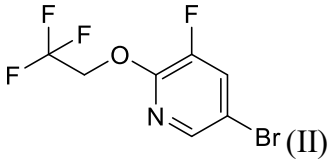
with hydrazine;

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;

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


(II)

with a palladium catalyst and bis(pinacolato)diboron.

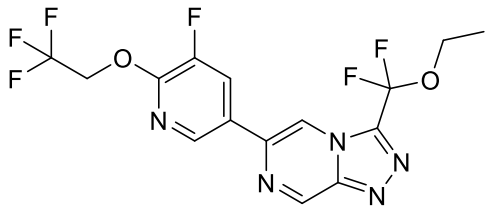
Described herein are compositions or dosage forms useful for preventing and/or treating a disease, disorder, or condition, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, e.g., abnormal late sodium current (INaL). The present disclosure also comprises methods 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.

Claims

1. A composition comprising:

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



; and a pharmaceutically acceptable excipient;

wherein the composition is in the form of a capsule or a blend;

wherein the pharmaceutically acceptable excipient is a filler; and

wherein the pharmaceutical composition comprises:

from 50% to 90% by weight filler and

from 0% to 5% by weight lubricant; or

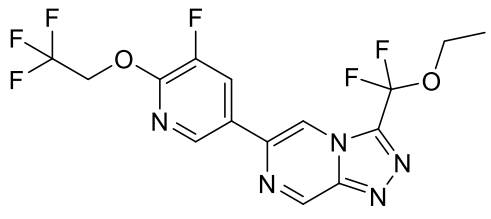
from 1% to 50% by weight Compound 1;

from 50% to 90% by weight filler; and

from 0% to 4% by weight lubricant.

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

wherein the composition is in the form of a capsule or a blend;

wherein the pharmaceutically acceptable excipient is a filler; and

wherein the pharmaceutical composition comprises:

from 50% to 90% by weight filler and

from 0% to 5% by weight lubricant; or

from 1% to 50% by weight Compound 1;

from 50% to 90% by weight filler; and

from 0% to 4% by weight lubricant.

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

4. The composition of any one of claims 1-3, wherein the composition is for oral administration.

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

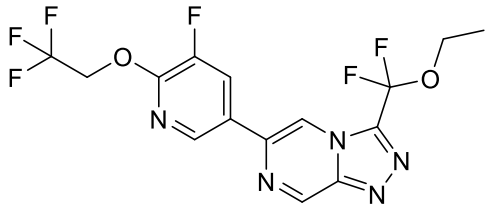
6. The composition of claim 5, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 12.6±0.2, 15.8±0.2, and 18.6±0.2; or wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following 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; or wherein 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 filler is microcrystalline cellulose or starch.

8. The composition of any one of claims 1-7, wherein the ratio of Compound 1 to the filler is 1:1 or 1:10.

9. A composition comprising:

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



; and

a pharmaceutically acceptable excipient;

wherein the composition is in a liquid form;

wherein the composition comprises:

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

from 5% to 15% by weight an emulsifier (e.g., Kolliphor RH40); and

from 40% to 60% by weight water;

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

wherein the composition comprises:

from 55% to 60% by weight an emulsifier (e.g., Kolliphor RH40);

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

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

from 15% to 20% by weight ethanol;

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

wherein the composition comprises:

from 65% to 70% by weight an emulsifier (e.g., Kolliphor RH40);

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

from 7% to 12% by weight propylene glycol;

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

wherein the composition comprises:

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

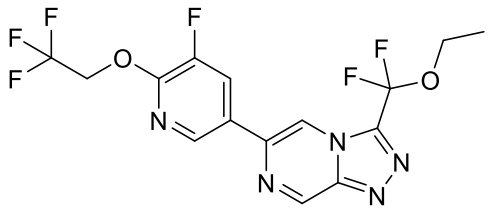
from 5% to 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin (e.g., Vitamin ETPGS)); and

from 40% to 60% by weight water;

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

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

wherein the composition is in a liquid form;

wherein the composition comprises:

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

from 5% to 15% by weight an emulsifier (e.g., Kolliphor RH40); and

from 40% to 60% by weight water;

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

wherein the composition comprises:

from 55% to 60% by weight an emulsifier (e.g., Kolliphor RH40);

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

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

from 15% to 20% by weight ethanol;

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

wherein the composition comprises:

from 65% to 70% by weight an emulsifier (e.g., Kolliphor RH40);

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

from 7% to 12% by weight propylene glycol;

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

wherein the composition comprises:

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

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

from 40% to 60% by weight water;

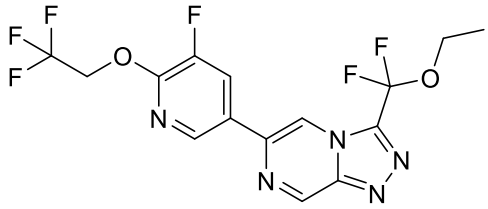
wherein the concentration of Compound 1 is from 1 mg/mL to 5 mg/mL or from 0.5 mg/mL to 2.5 mg/mL.

11. The composition of claim 9 or 10, wherein the composition is in the form of a solution.

12. The composition of claim 11, wherein the pharmaceutically acceptable excipient is selected from the group consisting of a co-solubilizer/co-solvent (e.g., polymer (e.g., PEG 400)), an emulsifier (e.g., Kolliphor RH40), a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), a vitamin (e.g., Vitamin ETPGS)), and a solvent (e.g., propylene glycol, ethanol, diethylene glycol monoethyl ether (or Transcutol HP)).

13. A composition comprising:

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


; and a pharmaceutically acceptable excipient;

wherein the composition is in the form of a suspension; optionally wherein the concentration of Compound 1 is 0.1 mg/mL, 0.5 mg, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 15 mg/mL of Compound 1; and

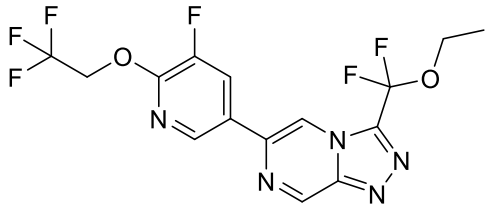
wherein the pharmaceutically acceptable excipient comprises:

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

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

14. 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 0.1 mg to 500 mg (e.g., from 0.5 mg to 200 mg, from 1 mg to 150 mg, from 10 mg to 120 mg, from 10 mg to 150 mg, from 20 mg to 150 mg, from 70 mg to 120 mg, from 30 mg to 60 mg, 100 mg, or 50 mg);

wherein the composition is in the form of a suspension; optionally wherein the concentration of Compound 1 is 0.1 mg/mL, 0.5 mg, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 15 mg/mL of Compound 1; and

wherein the pharmaceutically acceptable excipient comprises:

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

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

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

16. The composition of any one of claims 1-15, 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.

17. Use of the composition of any one of claims 1-16 in the manufacture of a medicament for treating a condition wherein the condition is a neurological or psychiatric disorder.

18. The use of claim 17, 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.

19. The use of claim 17, 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, and 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 mutation, epileptic encephalopathy with SCN2A mutation, epileptic encephalopathy with 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, sudden unexpected death in epilepsy (SUDEP), Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

20. Use of the composition of any one of claims 1-16 in the manufacture of a medicament for treating cancer.

21. Use of the composition of any one of claims 1-15 in the manufacture of a medicament for treating a neurological disorder, a psychiatric disorder, pain or cancer in a subject in need thereof.

22. Use of the composition of any one of claims 1-15 in the manufacture of a medicament for treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof.

23. The use of claim 22, 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.

24. Use of the composition of any one of claims 1-15 in the manufacture of a medicament for treating or preventing a migraine in a subject in need thereof.

25. The use of claim 24, 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.

26. Use of the composition of any one of claim 1-15 in the manufacture of a medicament for treating or preventing cortical spreading depression (CSD) in a subject in need thereof.

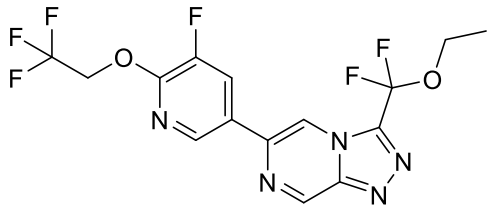
27. Use of the composition of any one of claims 1-15 in the manufacture of a medicament for treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof.

28. The use of claim 27, 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.

29. The use of any one of claims 17-28, 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.

30. The composition of any one of claims 1-21 for use in therapy.

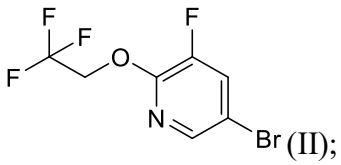
31. A method of making Compound 1:



,

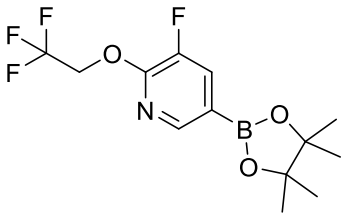
or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

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



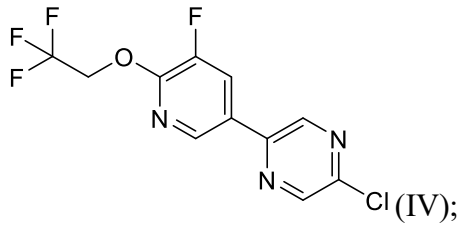
(II);

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

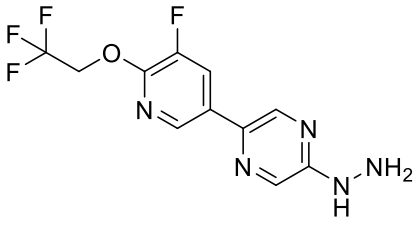


(III);

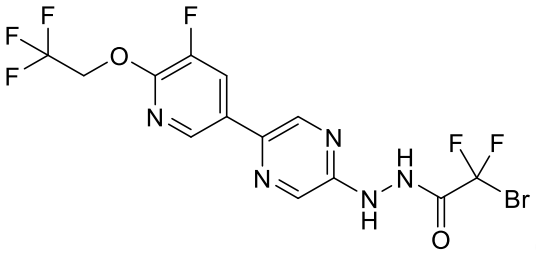
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

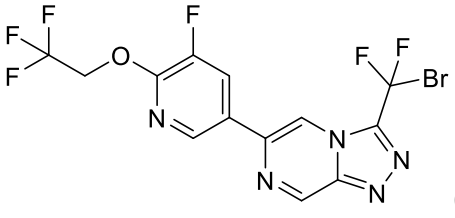
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(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

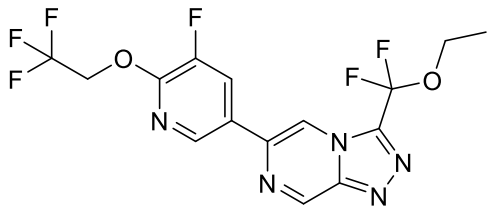
(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

32. The method of claim 31, wherein the palladium catalyst in step (ii) or (iii) is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

33. The method of claim 31 or 32, wherein the silver catalyst in step (vii) is silver tetrafluoroborate.

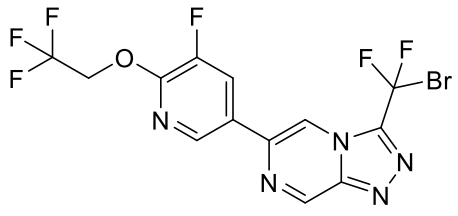
34. The method of any one of claims 31-33, wherein the acid in step (vi) is *p*-toluenesulfonic acid.

35. A method of making Compound 1:



(I)

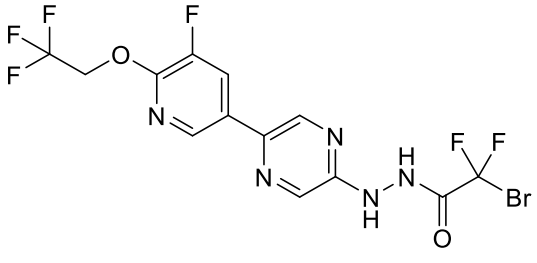
or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):



(VII)

with a silver catalyst and ethanol;

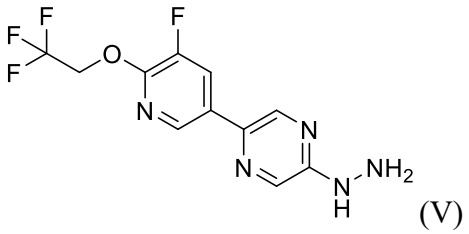
wherein the compound of formula (VII) is provided by contacting the compound of formula (VI):



(VI)

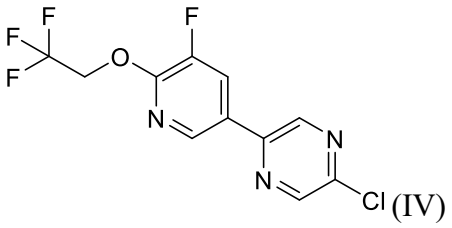
with an acid;

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


(V)

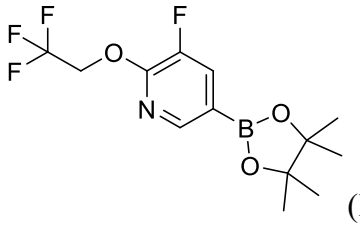
with 2-bromo-2,2-difluoro-acetyl chloride;

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


(IV)

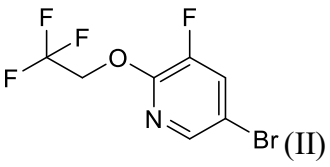
with hydrazine;

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;

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


(II)

with a palladium catalyst and bis(pinacolato)diboron.

36. The method of claim 35, wherein the compound of formula (II) is provided by contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine.

37. The method of claim 35 or 36, wherein the silver catalyst is silver tetrafluoroborate.

38. The method of any one of claims 35-37, wherein the acid is *p*-toluenesulfonic acid.

39. The method of any one of claims 35-38, wherein the palladium catalyst is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.