CLAIMS

1. A pharmaceutical composition comprising a metal channel activator and a glutamate modulator.

2. The pharmaceutical composition of Claim 1, wherein the metal channel activator is a potassium channel activator.

3. The pharmaceutical composition of Claim 2, wherein the potassium channel activator is a Kv7 channel activator,

optionally wherein the Kv7 channel activator is a Kv7.1 channel activator, a Kv7.2 channel activator, a Kv7.3 channel activator, a Kv7.4 channel activator, a Kv7.5 channel activator, or any combination thereof,

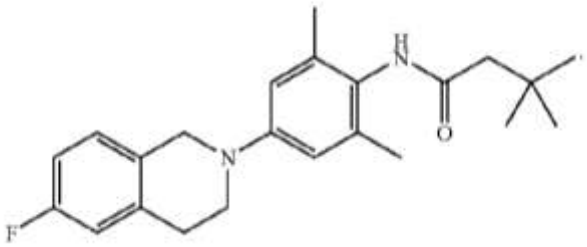
optionally wherein the Kv7 channel activator is a Kv7.2/7.3 channel activator.

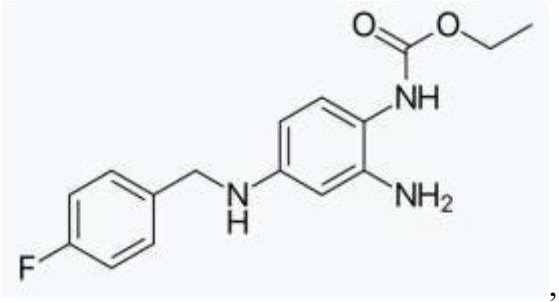
4 The pharmaceutical composition of any one of claims 1 to 3, wherein the metal channel activator is selected from one or more compounds according to any one or more of formulas 1 to 171.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the glutamate modulator is selected from one or more compounds according to any one or more of formulas 200 to 463.

6. The pharmaceutical composition of any one of claims 1 to 3, wherein the glutamate modulator is selected from one or more compounds according to any one or more of formulas 200 to 463, and wherein the metal channel activator is selected from one or more of the disclosed compounds according to any one or more of formulas 1 to 171.

7. The pharmaceutical composition of any one of claims 1 to 6, wherein the metal channel activator is

(a) , or a pharmaceutically acceptable salt thereof, and/or

(b) , of or a pharmaceutically acceptable salt thereof.

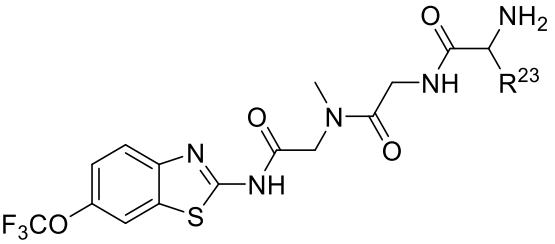
8. The pharmaceutical composition of any one of claims 1 to 7, wherein the glutamate modulator is riluzole, memantine, n-acetlcysteine, amantadine, topiramate, pregabalin, lamotrigine, ketamine, s-ketamine, AZD8108, AZD6765 (lanicemine), BHV-4157 (troriluzole), dextromethorphan, AV-101, CERC-301, GLY-13, and pharmaceutically acceptable salts, prodrugs or analogs thereof,

optionally wherein the glutamate modulator or a pharmaceutically acceptable salt thereof is in a form of a prodrug,

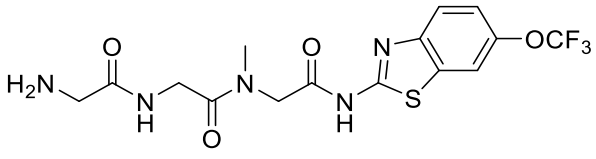
optionally wherein the glutamate modulator is riluzole or a pharmaceutically acceptable salt thereof,

optionally wherein the riluzole or a pharmaceutically acceptable salt thereof is in a form of a prodrug.

9. The pharmaceutical composition of Claim 9, wherein the prodrug of riluzole has the following structure:

(a) 

wherein R_{23} is selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CCH, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2OH, CH_2OCH_2Ph, $CH_2CH_2OCH_2Ph$, $CH(OH)CH_3$, CH_2Ph, CH_2(cyclohexyl), CH_2(4-OH-Ph), $(CH_2)_4NH_2$, $(CH_2)_3NHC(NH_2)NH$, CH_2(3-indole), CH_2(5-imidazole), CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2CONH_2, and $CH_2CH_2CONH_2$, and/or

(b) 

10. Use of the pharmaceutical composition of any one of claims 1-9 in the manufacture of a medicament for treating a depressive disorder.

11. The use of Claim 10, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated

with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

12. Use of the pharmaceutical composition of any one of claims 1-9 in the manufacture of a medicament for treating a neurological or neurodegenerative disorder.

13. The use of Claim 12, wherein neurological or neurodegenerative disorder is amyotrophic lateral sclerosis, bipolar disorder, treatment resistant and major depression, general anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, dementia, agitation, apathy, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, Rett syndrome, eating disorders, conduct disorder, neurodegenerative disorders, pain disorders, post-traumatic stress disorder (PTSD), supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer’s disease, drug addiction, tinnitus, mental retardation, obsessive-compulsive disorder, spinal muscular atrophy, radiation therapy, multiple sclerosis, chronic cerebellar ataxia, spinocerebellar ataxia (SCA), cervical spondylotic myelopathy, spinal cord injury, hereditary cerebellar ataxia, Tourette syndrome, autism spectrum disorder, schizophrenia, fragile X syndrome, Parkinson's Disease, Huntington’s disease, or any combination thereof.

14. Use of the pharmaceutical composition of any one of claims 1-9 in the manufacture of a medicament for treating a pain disorder.

15. The use of Claim 14, wherein the pain disorder is acute pain, chronic pain, neuropathic pain, nociceptive pain, radicular pain,

optionally wherein the pain disorder is migraine, inflammatory pain, persistent pain, cancer pain, and postoperative pain.

16. A kit for treating a patient afflicted with a disorder in which a metal channel activator is clinically relevant, said kit including:

(a) a metal channel activator according to any one of Formulas 1 to 171; and

(b) instructions for administering said metal channel activator in combination with a glutamate modulator by one of the methods of Claims 10-15.

17. A kit for treating a patient afflicted with a disorder in which a glutamate modulator is clinically relevant, said kit including:

(a) a glutamate modulator according to any one of claims 200 to 463; and

(b) instructions for administering said glutamate modulator with a metal channel activator by one of the methods of Claims 10-15.

18. A pharmaceutical composition comprising a glutamate modulator according to one of Formula 200 to 202 and the metal channel activator is a compound according to one of Formula 1 to 5.

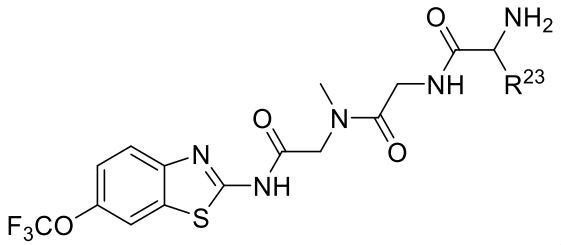
19. The pharmaceutical composition of claim 18, wherein the glutamate modulator is a compound according to Formula 200 and the metal channel activator is a compound according to Formula 2,

optionally wherein the glutamate modulator is a compound according to Formula 200 and the metal channel activator is a compound according to any one of Formula 2-1, Formula 2-2, Formula 2-3, Formula 2-4, Formula 2-5, Formula 2-6, Formula 2-7, Formula 2-8, Formula 2-9, or Formula 2-10,

optionally wherein the glutamate modulator is a compound according to Formula 200 and the metal channel activator is a compound according to Formula 4,

optionally wherein the glutamate modulator is a compound according to Formula 201 and the metal channel activator is a compound according to Formula 5.

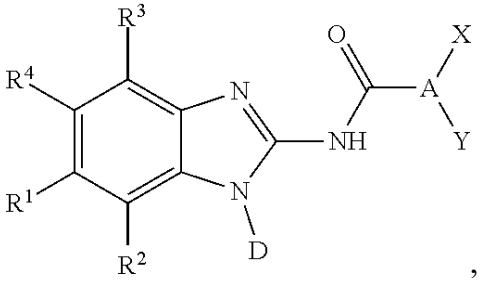
20. A pharmaceutical composition comprising: a glutamate modulator according to:



,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

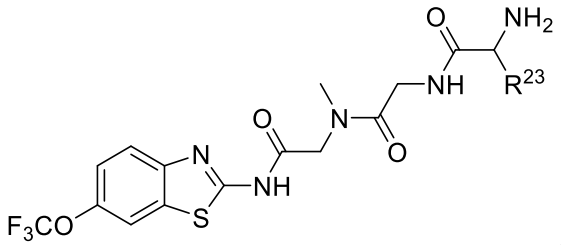
a metal channel activator according to:



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wherein D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, optionally substituted pyridinyl, isopropyl, or t-butyl; A is C_{2-8} alkyl; X is H, F, CF_3 optionally substituted phenyl, or optionally substituted pyridinyl; Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; R^1 is F, Cl, Br, CN, OCH_3, CHF_2, CF_3, C_{1-4} —CO_2-alkyl, C_{1-4} alkyl, —CH_2CO_2H, —$CH_2CO_2CH_2CH_3$ or —$CH_2CON(CH_3)_2$, or C_{1-5} hydroxyalkyl; and R^2, R^3, and R^4 are independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br, including pharmaceutically acceptable salts thereof.

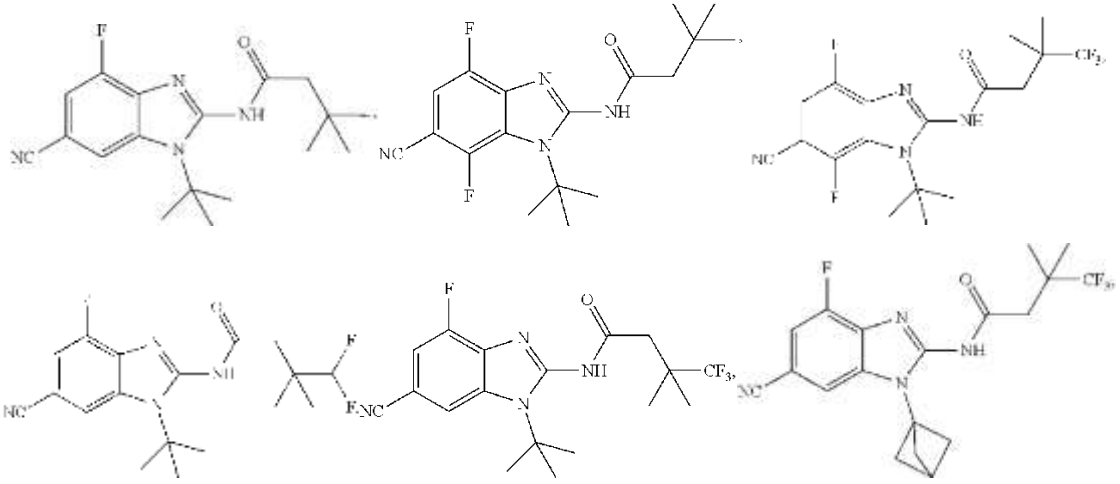
21. A pharmaceutical composition comprising: a glutamate modulator according to:



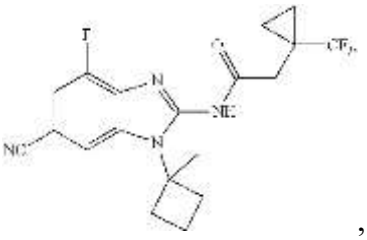
,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

a metal channel activator according to any of:

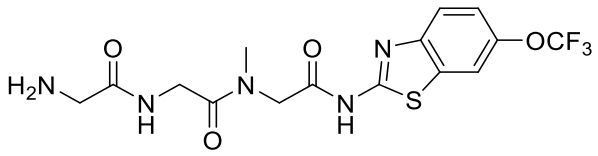


and



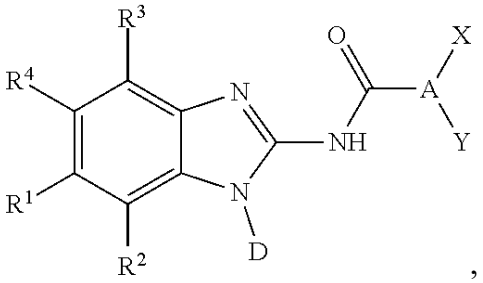
, including pharmaceutically acceptable salts thereof.

22. A pharmaceutical composition comprising: a glutamate modulator according to:



including pharmaceutically acceptable salts thereof; and

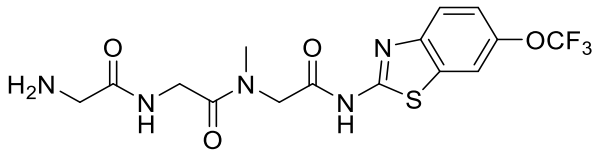
a metal channel activator according to:



,

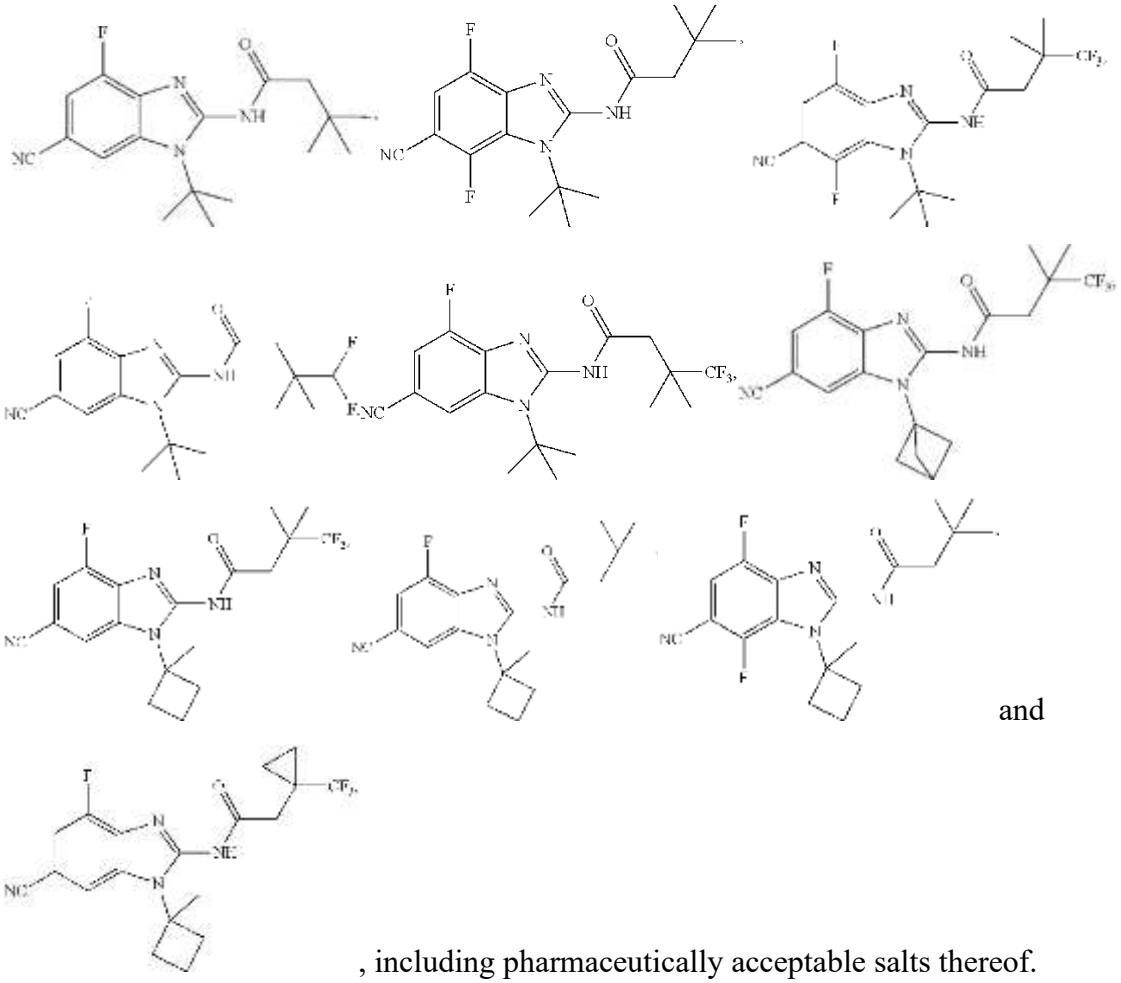
wherein D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, optionally substituted pyridinyl, isopropyl, or t-butyl; A is C_{2-8} alkyl; X is H, F, CF_3 optionally substituted phenyl, or optionally substituted pyridinyl; Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; R^1 is F, Cl, Br, CN, OCH_3, CHF_2, CF_3, C_{1-4} —CO_2-alkyl, C_{1-4} alkyl, —CH_2CO_2H, —$CH_2CO_2CH_2CH_3$ or —$CH_2CON(CH_3)_2$, or C_{1-5} hydroxyalkyl; and R^2, R^3, and R^4 are independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br, including pharmaceutically acceptable salts thereof.

23. A pharmaceutical composition comprising: a glutamate modulator according to:



including pharmaceutically acceptable salts thereof; and

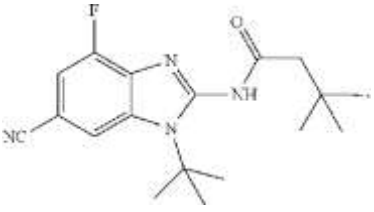
a metal channel activator according to any of:



and

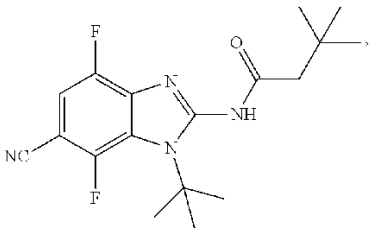
, including pharmaceutically acceptable salts thereof.

24. The pharmaceutical composition of any one of claims 20 to 23, wherein the metal channel activator is the compound



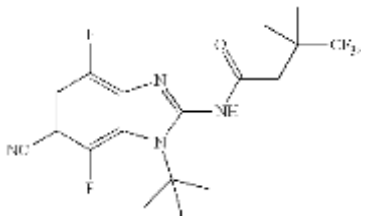
(a)

or a pharmaceutically acceptable salt thereof,

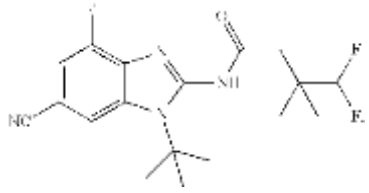


(b)

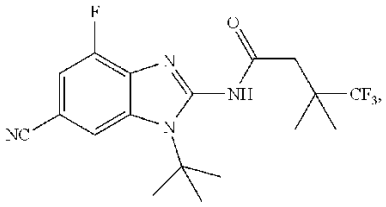
or a pharmaceutically acceptable salt thereof,

(c) 

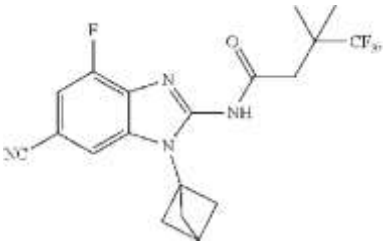
or a pharmaceutically acceptable salt thereof,

(d) 

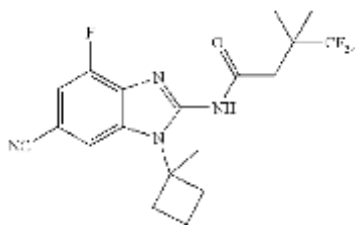
or a pharmaceutically acceptable salt thereof,

(e) 

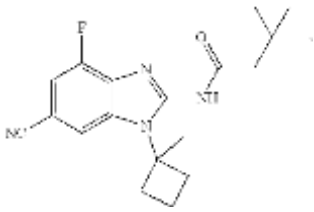
or a pharmaceutically acceptable salt thereof,

(f) 

or a pharmaceutically acceptable salt thereof,

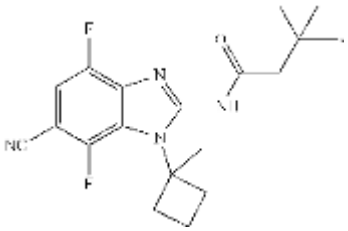
(g) 

or a pharmaceutically acceptable salt thereof.



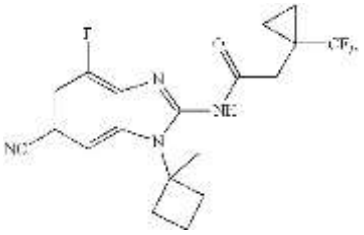
(h)

or a pharmaceutically acceptable salt thereof,



(i)

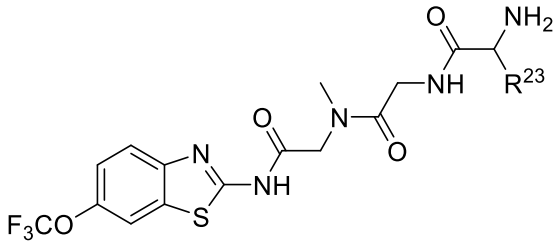
or a pharmaceutically acceptable salt thereof, and/or



(j)

or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising: a glutamate modulator according to:

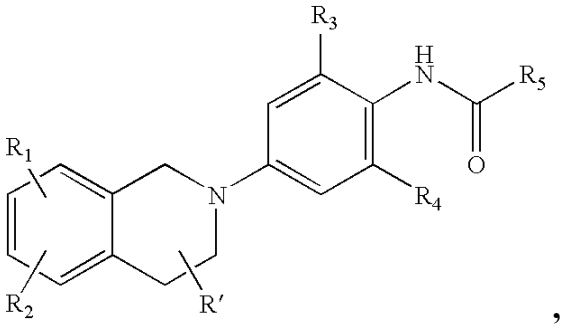


,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2,

(CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

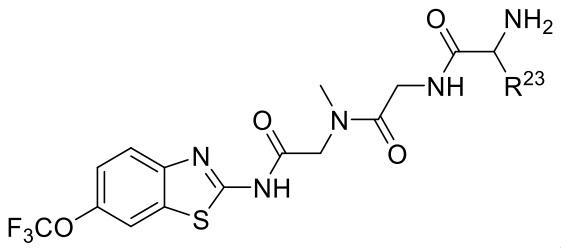
a metal channel activator according to:



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wherein, R_1 is selected from the group consisting of H, halogen, CN, CH_2CN, CF_3, C_1-C_6 alkyl, OCH_3, $(C{=}O)OCH_3$, $O(C{=}O)CH_3$, OCF_3, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, and pyridyl; R_2 is selected from the group consisting of H, F, OCH_3, CH_3, and CF_3; R_3 and R_4 vary independently, and are selected from the group consisting of H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; and R_5 is selected from the group consisting of C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, $CR_6{=}CH{-}C_3$-C_6 cycloalkyl, $CH{=}CR_6{-}C_3$-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, $(CHR_6)_wCH_2Ar$, and CH_2-$C(CH_3)_3$;wherein w=0-3; Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; R′ is selected from the group consisting of H, CH_3, CH_2CH_3, or halogen; wherein all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from the group consisting of C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3, including pharmaceutically acceptable salts thereof.

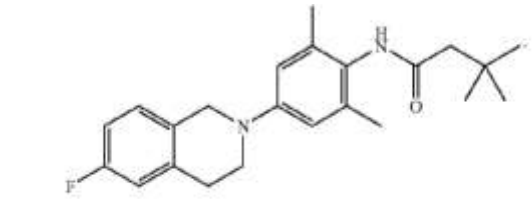
26. A pharmaceutical composition comprising: a glutamate modulator according to:



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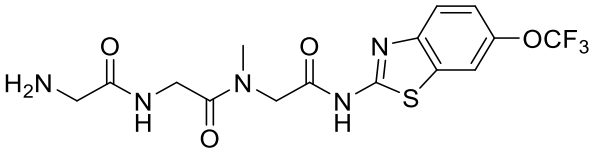
wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

a metal channel activator according to:



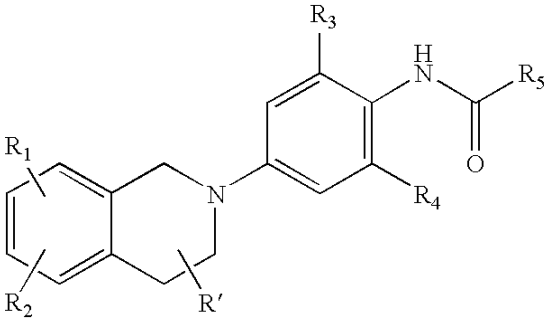
, including pharmaceutically acceptable salts thereof.

27. A pharmaceutical composition comprising: a glutamate modulator according to:



including pharmaceutically acceptable salts thereof; and

a metal channel activator according to:

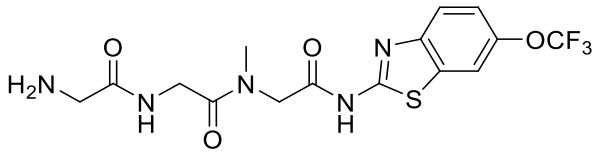


,

wherein, R_1 is selected from the group consisting of H, halogen, CN, CH_2CN, CF_3, C_1-C_6 alkyl, OCH_3, (C═O)OCH_3, O(C═O)CH_3, OCF_3, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, and pyridyl; R_2 is selected from the group consisting of H, F, OCH_3, CH_3, and CF_3; R_3 and R_4 vary independently, and are selected from the group consisting of H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; and R_5 is selected from the group consisting of C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6═CH—C_3-

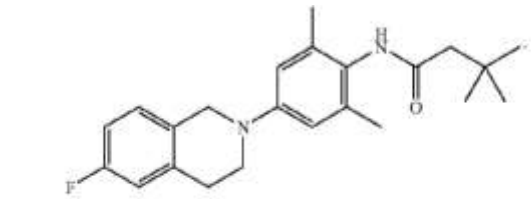
C_6 cycloalkyl, CH═CR_6—C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, $(CHR_6)_wCH_2Ar$, and CH_2-$C(CH_3)_3$;wherein w=0-3; Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; R′ is selected from the group consisting of H, CH_3, CH_2CH_3, or halogen; wherein all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from the group consisting of C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3, including pharmaceutically acceptable salts thereof.

28. A pharmaceutical composition comprising: a glutamate modulator according to:



including pharmaceutically acceptable salts thereof; and

a metal channel activator according to:



, including pharmaceutically acceptable salts thereof.

29. The pharmaceutical composition of any one of claims 18 – 28, wherein the ratio of the metal channel activator to glutamate modulator by weight ranges from about 1:30 to about 1:1,

optionally wherein the ratio of the metal channel activator to glutamate modulator by weight is about 1:4.

30. Use of the pharmaceutical composition of any one of claims 18-28 in the manufacture of a medicament for treating a depressive disorder.

31. The use of Claim 30, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

32. Use of the pharmaceutical composition of any one of claims 18-28 in the manufacture of a medicament for treating a neurological or neurodegenerative disorder.

33. The use of Claim 32, wherein neurological or neurodegenerative disorder is amyotrophic lateral sclerosis, bipolar disorder, treatment resistant and major depression, general anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, dementia, agitation, apathy, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, Rett syndrome, eating disorders, conduct disorder, neurodegenerative disorders, pain disorders, post-traumatic stress disorder (PTSD), supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer’s disease, drug addiction, tinnitus, mental retardation, obsessive-compulsive disorder, spinal muscular atrophy, radiation therapy, multiple sclerosis, chronic cerebellar ataxia, spinocerebellar ataxia (SCA), cervical spondylotic myelopathy, spinal cord injury, hereditary cerebellar ataxia, Tourette syndrome, autism spectrum disorder, schizophrenia, fragile X syndrome, Parkinson's Disease, Huntington’s disease, or any combination thereof.

34. Use of the pharmaceutical composition of any one of claims 18-28 in the manufacture of a medicament for treating a pain disorder.

35. The use of Claim 34, wherein the pain disorder is acute pain, chronic pain, neuropathic pain, nociceptive pain, radicular pain,

optionally wherein the pain disorder is migraine, inflammatory pain, persistent pain, cancer pain, and postoperative pain.

36. A kit for treating a patient afflicted with a disorders in which a metal channel activator is clinically relevant, said kit including:

(a) the metal channel activator; and

(b) instructions for administering said metal channel activator in combination with a glutamate modulator by one of the methods of Claims 30-35.

37. A kit for treating a patient afflicted with a disorder in which a glutamate modulator is clinically relevant, said kit including:

(a) the glutamate modulator; and

(b) instructions for administering said glutamate modulator with a metal channel activator by one of the methods of Claims 30-35.

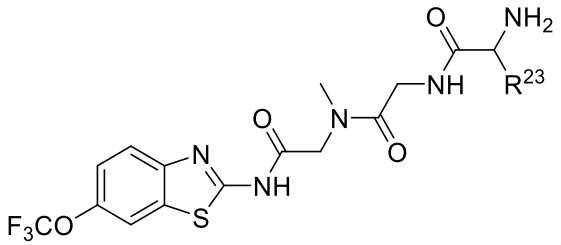
38. Use of one or more metal channel activators according to Formula 1 to 171; and one or more glutamate modulators according to Formula 200 to 463 in the manufacture of a medicament for treating a depressive disorder;.

39. Use of one or more metal channel activators according to Formula 1 to 171; and one or more glutamate modulators according to Formula 200 to 463 in the manufacture of a medicament for treating a neurological or neurodegenerative disorder.

40. Use of one or more metal channel activators according to Formula 1 to 171; and one or more glutamate modulators according to Formula 200 to 463 in the manufacture of a medicament for treating pain or a pain disorder.

41. The use of any one of claims 38 to 40, wherein:

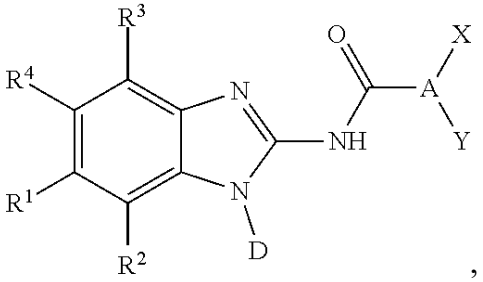
(a) the glutamate modulator is a compound according to:



,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

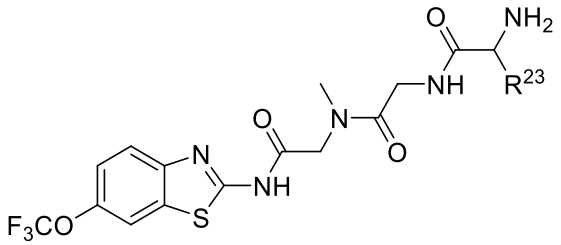
the metal channel activator is a compound according to:



,

wherein D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, optionally substituted pyridinyl, isopropyl, or t-butyl; A is C_{2-8} alkyl; X is H, F, CF_3 optionally substituted phenyl, or optionally substituted pyridinyl; Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; R^1 is F, Cl, Br, CN, OCH_3, CHF_2, CF_3, C_{1-4} —CO_2-alkyl, C_{1-4} alkyl, —CH_2CO_2H, —$CH_2CO_2CH_2CH_3$ or —$CH_2CON(CH_3)_2$, or C_{1-5} hydroxyalkyl; and R^2, R^3, and R^4 are independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br, including pharmaceutically acceptable salts thereof,

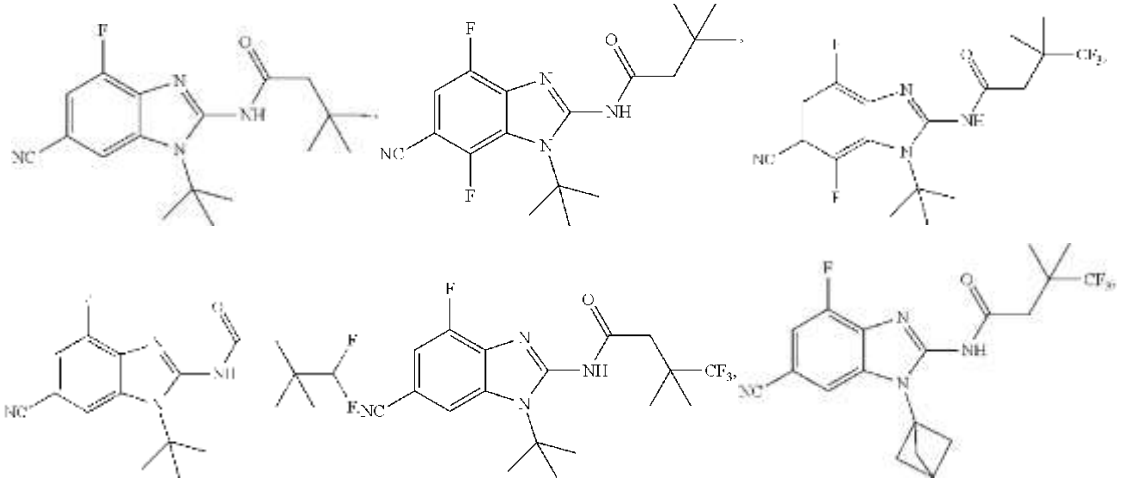
(b) the glutamate modulator is a compound according to:



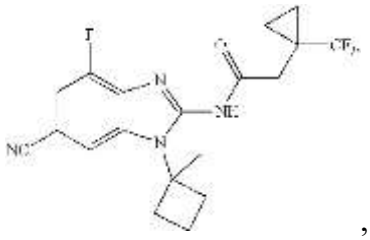
,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

the metal channel activator is a compound selected from:

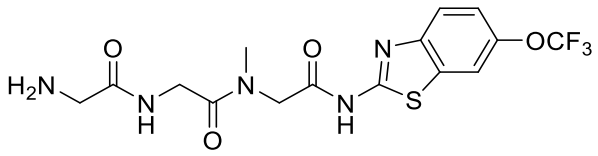


and



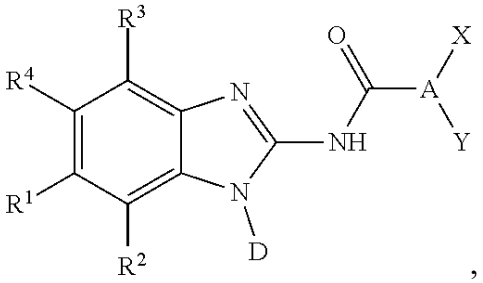
, including pharmaceutically acceptable salts thereof,

(c) the glutamate modulator is a compound according to:



including pharmaceutically acceptable salts thereof; and

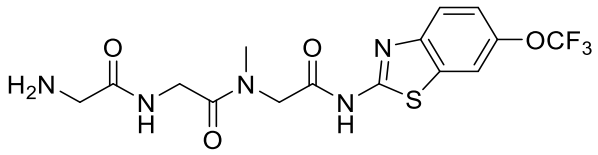
the metal channel activator is a compound according to:



,

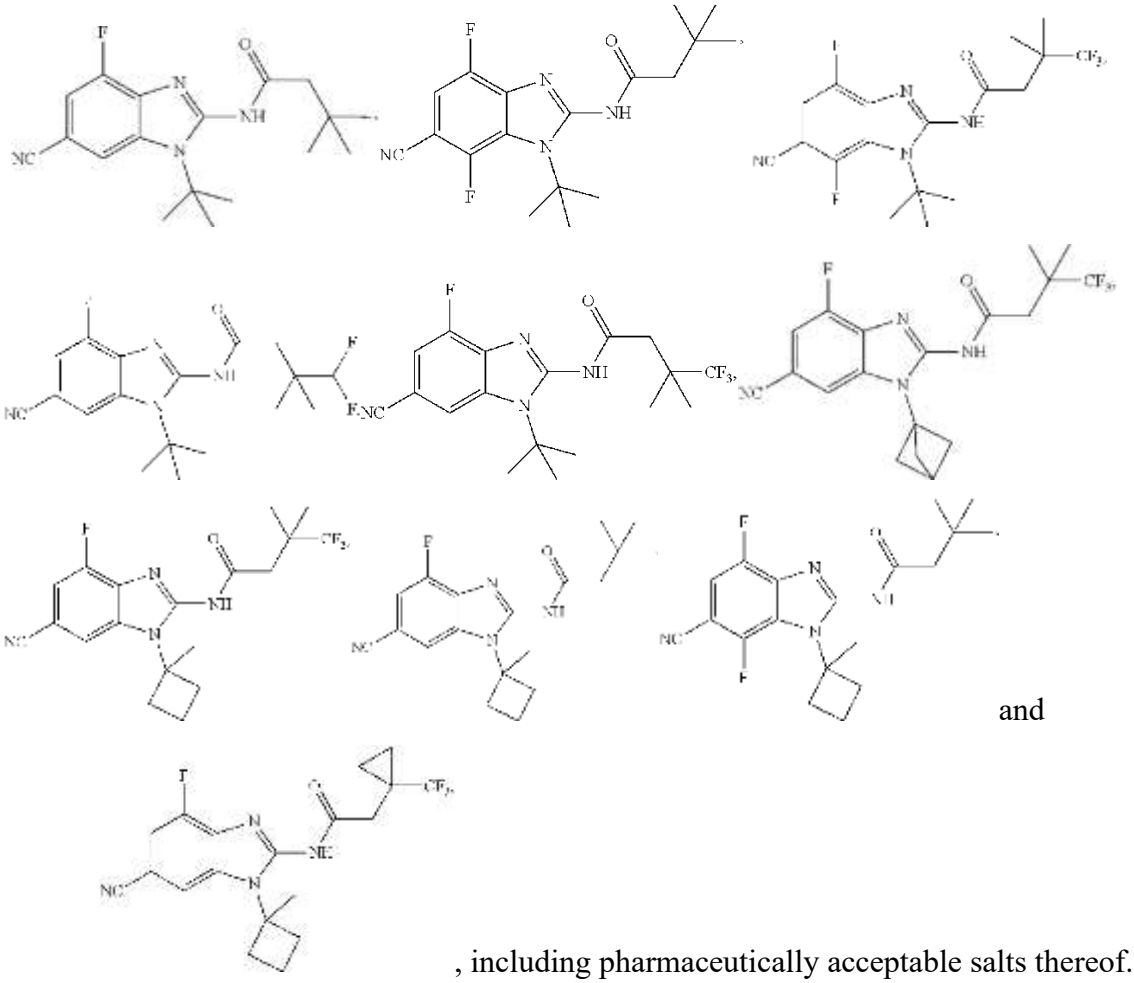
wherein D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, optionally substituted pyridinyl, isopropyl, or t-butyl; A is C_{2-8} alkyl; X is H, F, CF_3 optionally substituted phenyl, or optionally substituted pyridinyl; Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; R^1 is F, Cl, Br, CN, OCH_3, CHF_2, CF_3, C_{1-4} —CO_2-alkyl, C_{1-4} alkyl, —CH_2CO_2H, —$CH_2CO_2CH_2CH_3$ or —$CH_2CON(CH_3)_2$, or C_{1-5} hydroxyalkyl; and R^2, R^3, and R^4 are independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br, including pharmaceutically acceptable salts thereof,

(d) the glutamate modulator is a compound according to:



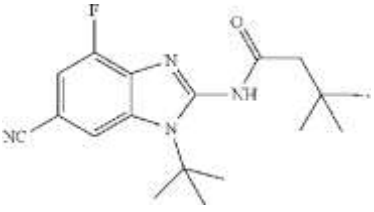
including pharmaceutically acceptable salts thereof; and

the metal channel activator is a compound selected from:

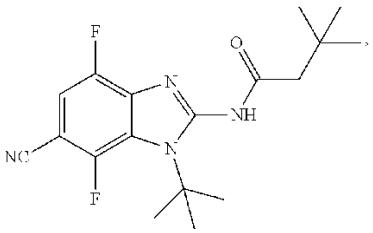

and

, including pharmaceutically acceptable salts thereof.

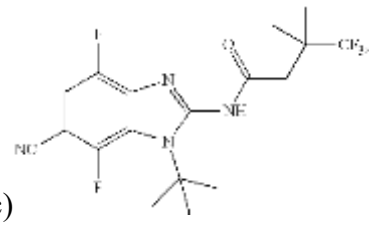
42. The use of any one of claims 38 – 41, wherein the metal channel activator is the compound


(a)

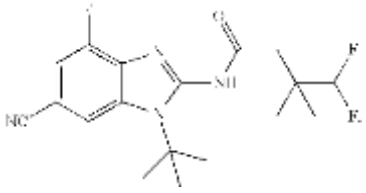
or a pharmaceutically acceptable salt thereof,

(b) 

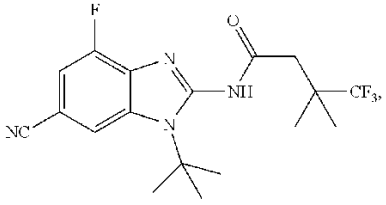
or a pharmaceutically acceptable salt thereof,

(c) 

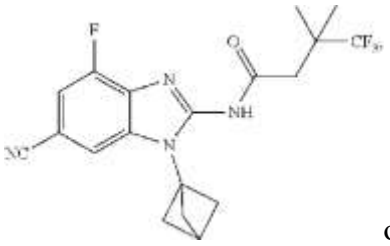
or a pharmaceutically acceptable salt thereof,

(d) 

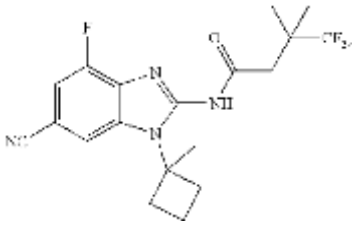
or a pharmaceutically acceptable salt thereof,

(e) 

or a pharmaceutically acceptable salt thereof,

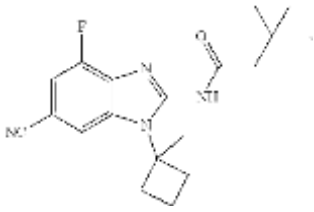
(f) 

or a pharmaceutically acceptable salt thereof,



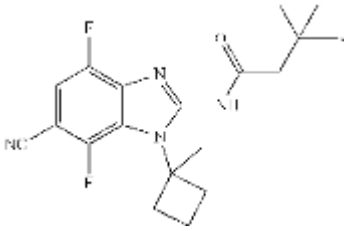
(g)

or a pharmaceutically acceptable salt thereof,



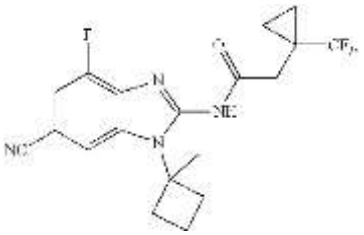
(h)

or a pharmaceutically acceptable salt thereof,



(i)

or a pharmaceutically acceptable salt thereof, and/or

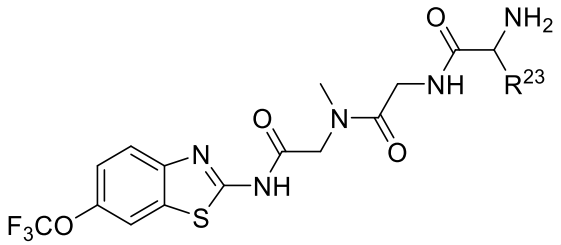


(j)

or a pharmaceutically acceptable salt thereof.

43. The use of any one of claims 38 to 40, wherein:

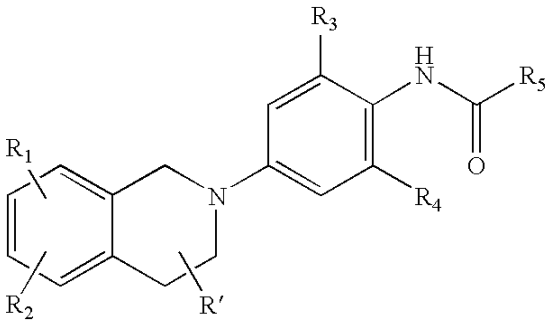
(a) the glutamate modulator is a compound according to:



,

wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

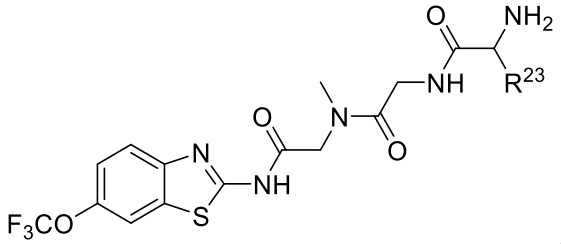
the metal channel activator is a compound according to:



,

wherein, R_1 is selected from the group consisting of H, halogen, CN, CH_2CN, CF_3, C_1-C_6 alkyl, OCH_3, (C═O)OCH_3, O(C═O)CH_3, OCF_3, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, and pyridyl; R_2 is selected from the group consisting of H, F, OCH_3, CH_3, and CF_3; R_3 and R_4 vary independently, and are selected from the group consisting of H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; and R_5 is selected from the group consisting of C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6═CH—C_3-C_6 cycloalkyl, CH═CR_6—C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, $(CHR_6)_wCH_2Ar$, and CH_2-$C(CH_3)_3$;wherein w=0-3; Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; R′ is selected from the group consisting of H, CH_3, CH_2CH_3, or halogen; wherein all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from the group consisting of C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3, including pharmaceutically acceptable salts thereof,

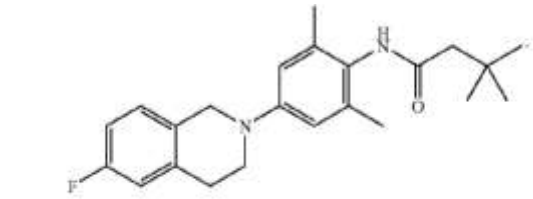
(b) the glutamate modulator is a compound according to:



,

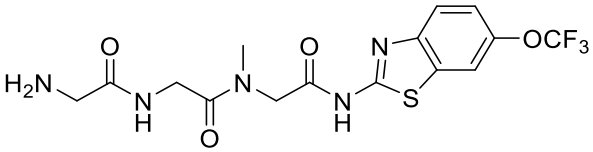
wherein R23 is selected from the group consisting of H, CH3, CH2CH3, CH2CH2CH3, CH2CCH, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3, CH2OH, CH2OCH2Ph, CH2CH2OCH2Ph, CH(OH)CH3, CH2Ph, CH2(cyclohexyl), CH2(4-OH-Ph), (CH2)4NH2, (CH2)3NHC(NH2)NH, CH2(3-indole), CH2(5-imidazole), CH2CO2H, CH2CH2CO2H, CH2CONH2, and CH2CH2CONH2, including pharmaceutically acceptable salts thereof; and

the metal channel activator is a compound according to:



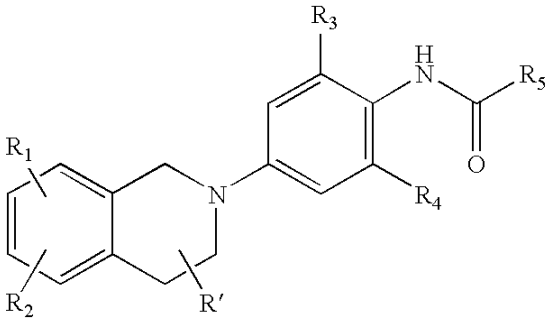
, including pharmaceutically acceptable salts thereof,

(c) the glutamate modulator is a compound according to:



including pharmaceutically acceptable salts thereof; and

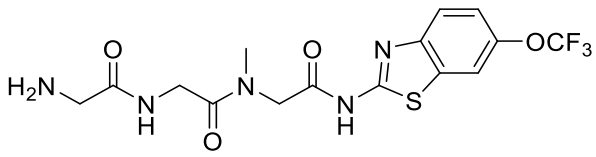
the metal channel activator is a compound according to:



,

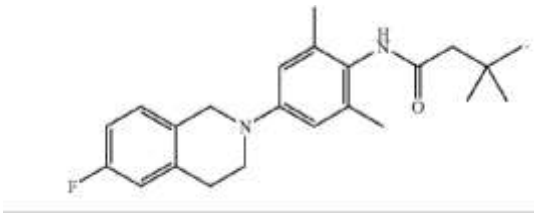
wherein, R_1 is selected from the group consisting of H, halogen, CN, CH_2CN, CF_3, C_1-C_6 alkyl, OCH_3, (C═O)OCH_3, O(C═O)CH_3, OCF_3, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, and pyridyl; R_2 is selected from the group consisting of H, F, OCH_3, CH_3, and CF_3; R_3 and R_4 vary independently, and are selected from the group consisting of H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; and R_5 is selected from the group consisting of C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6═CH—C_3-C_6 cycloalkyl, CH═CR_6—C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, $(CHR_6)_wCH_2Ar$, and CH_2-$C(CH_3)_3$;wherein w=0-3; Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; R′ is selected from the group consisting of H, CH_3, CH_2CH_3, or halogen; wherein all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from the group consisting of C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3, including pharmaceutically acceptable salts thereof, and/or

(d) the glutamate modulator is a compound according to:



including pharmaceutically acceptable salts thereof; and

the metal channel activator is a compound according to:



, including pharmaceutically acceptable salts thereof.

44. The use of any one of claims 38 to 43, wherein the metal channel activator and glutamate modulator are to be administered at a ratio ranging from about 1:30 to 1:1 by weight,

optionally wherein the ratio of metal channel activator to glutamate modulator is about 1:4 by weight.