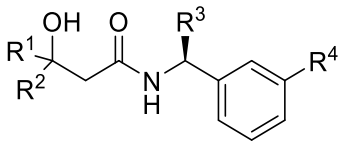
CLAIMS

1. A compound of Formula I



Formula I;

wherein

R1 is selected from the group consisting of C_1-C_6 alkyl, CF_3, CH_2CF_3, CF_2CHF_2, C_3-C_8 cycloalkyl, wherein said C_3-C_8 cycloalkyl may be substituted with 1 or 2 substituents selected from the group consisting of C_1-C_3 alkyl, F, CHF_2 and CF_3; and

R2 is H, C_1-C_6 alkyl or CF_3; or

R1 and R2 combine to form C_3-C_5 cycloalkyl optionally substituted with 1 or 2 F, CHF_2 or CF_3; ~~and~~

R3 is C_1-C_3 alkyl or CH_2O-C_{1-3} alkyl, said C_1-C_3 alkyl or CH_2O-C_1-C_3 is alkyl substituted with C≡N, 3 F or C_3-C_5 cycloalkyl; and

R4 is selected from the group consisting of OCF_3~~,~~ or $OCHF_2$,

or a pharmaceutically acceptable salt ~~of any of these compounds~~thereof.

2. The compound ~~of~~ according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R4 is OCF_3 ~~or $OCHF_2$~~.

3. The compound according to any one of the ~~previous~~ preceding claims, or a pharmaceutically acceptable salt thereof, wherein R3 is selected from the group consisting of CH_2-O-CF_3~~,~~ ~~CH_2-O- cyclopropyl,~~and CH_2-C≡N.

4. The compound according to any one of the ~~previous~~ preceding claims, or a pharmaceutically acceptable salt thereof, wherein R1 is C_3-C_4 cycloalkyl optionally substituted with 1 or 2 C_1-C_3 alkyl, F, CHF_2 or CF_3.

5. The compound according to any one of the ~~previous~~ preceding claims, or a pharmaceutically acceptable salt thereof, wherein R1 and R2 combine to form cyclobutyl optionally substituted with 1 or 2 F~~ and R4 is OCF_3 or $OCHF_2$~~.

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

~~(S)-N-((R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;~~

(S)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((R)-1-(3-(trifluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)-3-hydroxy-4,4-dimethylpentanamide;

~~(R)-N-(2-cyclopropoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;~~

~~(R)-N-(2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;~~

(R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)acetamide; ~~or~~and

(S)-N-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide,

or a pharmaceutically acceptable salt ~~of any of these compounds~~thereof.

7. A compound selected from the group consisting of:

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-3-hydroxy-4,4-dimethyl-N-((S)-1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl) pentanamide;

(R)-3-hydroxy-4,4-dimethyl-N-((S)-1-(3-(2,2,2-trifluoroethoxy) phenyl)ethyl)pentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl) propanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(S)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-(difluoromethoxy) phenyl)butyl)-3-hydroxypropanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)acetamide;

(R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide;

(S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)butyl)acetamide;

(S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)acetamide;

(S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(trifluoromethoxy) phenyl)propyl)acetamide;

(S)-N-(3,3-difluoro-1-(3-(trifluoromethoxy)phenyl)propyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;

(R)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxybutanamide;

(S)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy) phenyl)ethyl)-3-hydroxybutanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;

(*S*)-3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(*R*)-3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(*R*)-3-(1-fluorocyclopropyl)-3-hydroxy-*N*-((*R*)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide; and (*S*)-3-(1-fluorocyclopropyl)-3-hydroxy-*N*-((*R*)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide, or a pharmaceutically acceptable salt ~~of any of these compounds~~thereof.

8. A pharmaceutical composition comprising a compound ~~of any one of~~according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

9. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of epilepsy, bipolar disorder, migraine, or schizophrenia.~~9. A method of treating a patient in the need thereof suffering from epilepsy, bipolar disorder, migraine or schizophrenia comprising administering to the subject a therapeutically effective amount of a compound of any of claims 1 to 7, or a pharmaceutically acceptable salt thereof.~~

10. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive

disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypical disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, or Alzheimer's disease.

~~10. A method of treating a patient in the need thereof suffering from psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypical disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease comprising administering to the subject a therapeutically effective amount of a compound of any of claims 1 to 7, or a pharmaceutically acceptable salt thereof.~~

~~11. Use of a compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, in therapy.~~

~~12. Use of a compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the treatment of epilepsy, bipolar disorder, migraine or schizophrenia.~~

~~13. Use of a compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the treatment of psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major~~

~~depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypical disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease.~~

~~14. A compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating epilepsy, bipolar disorder, migraine or schizophrenia.~~

~~15. A compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypical disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease.~~

~~16. The compound or the pharmaceutical salt thereof according to claims 1-7 or the pharmaceutical composition according to claim 16 for use in the treatment of epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures.~~

~~17. The compound or the pharmaceutical salt thereof according to claims 1-7 or the pharmaceutical composition according to claim 16, for use in the treatment of Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, or seizures related to stress, hormonal changes, drugs, alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances (such as hyponatraemia.~~

~~18. The compound or the pharmaceutical salt thereof according to claims 1-7 or the pharmaceutical composition according to claim 16, for use in the treatment epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration.~~

~~19. A method of treating a patient in the need thereof suffering from epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy or seizures comprising administering to the subject a therapeutically effective amount of a compound of any of~~

~~claims 1 to 7, or a pharmaceutically acceptable salt thereof.~~

~~20. A method of treating a patient in the need thereof suffering from Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, or seizures related to stress, hormonal changes, drugs, alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances (such as hyponatraemia)or for use in the treatment epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration comprising administering to the subject a therapeutically effective amount of a compound of any of claims 1 to 7, or a pharmaceutically acceptable salt thereof.~~

~~21. Use of a compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the treatment of epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures.~~

~~22. Use of a compound according to claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the treatment of for use in the treatment of Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome) , or seizures related to stress, hormonal changes, drugs, alcohol, infection, or metabolic disturbances (such as hyponatraemia, or for use in the treatment epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration.~~

~~23~~11. ~~A~~ Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, ~~for~~ in the manufacture of a medicament for ~~treating~~ treatment of epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures.

~~24~~12. ~~A~~ Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, ~~for~~ in the manufacture of a medicament for treatment of Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures,

Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE), ~~and~~ Benign Familial Neonatal Convulsions, ~~and other epileptic syndromes (such as~~ severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, seizures related to stress, hormonal changes, drugs, alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances, ~~)~~or ~~for use in the treatment~~ epileptic symptoms as part of neurogenerative disorders~~, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration~~.

13. The use according to claim 12, wherein the seizures related to metabolic disturbances is hyponatraemia.

14. The use according to claim 12, wherein the neurodegenerative disorder is Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, or fronto-temporal lobar degeneration.