Currently available anti-epileptic drugs do not solely affect glutamatergic transmission. Their mechanism of action is generally conceptualized as altering the balance between excitatory (glutamate-mediated) and inhibitory (GABA-mediated) transmission (Johannessen Landmark "Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy" CNS Drugs 2008, Vol. 22(1), pp. 27-47).

A significant limiting factor in the use of SV2A ligands is tolerability and side-effect profile. For example the effective dose of levetiracetam for partial onset seizures is dosed at 1000 mg, 2000 mg, and 3000 mg, given as twice-daily. The side effects reported for levetiracetam include aggressive or angry behavior, anxiety, change in personality, chills, cough or hoarseness, crying, depersonalization, diarrhea, dry mouth, euphoria, fever, general feeling of discomfort or illness, headache, hyperventilation, irregular heartbeats, irritability, joint pain, loss of appetite, lower back or side pain, mental depression, muscle aches and pains, nausea, painful or difficult urination, paranoia, quick to react or overreact emotionally, rapidly changing moods, restlessness, shaking, shivering, shortness of breath, sleepiness or unusual drowsiness, sore throat, stuffy or runny nose, sweating, trouble sleeping, unusual tiredness or weakness and vomiting. Thus, there is still a need to provide an effective treatment with a lower effective dose of levetiracetam and a more favourable side effect profile for the treatment of epilepsy and related disorders, not only in the adult but also in the pediatric population.

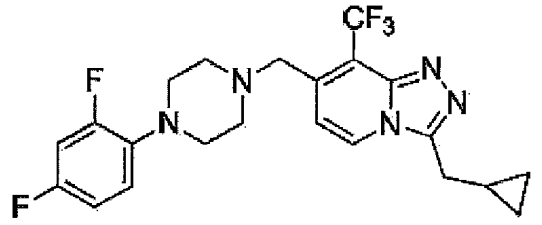
SUMMARY

In one aspect, there is provided a combination comprising

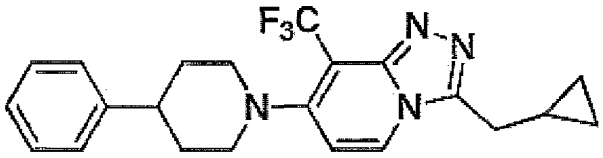
(a) a synaptic vesicle protein 2a ("SV2A") ligand selected from the group consisting of levetiracetam, brivaracetam and seletracetam; and

(b) a positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 selected from

1) a compound of Formula (I) selected from

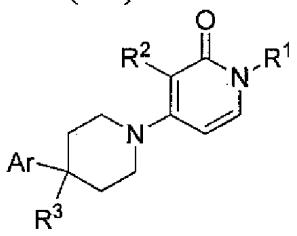


and



or a pharmaceutically acceptable salt or a solvate thereof;

2) a compound of Formula (I-A)



(I-A)

or a stereochemically isomeric form thereof, wherein

R^1 is C_{1-6}alkyl; or C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl or trifluoromethoxy;

R^2 is halo, trifluoromethyl, C_{1-3}alkyl or cyclopropyl;

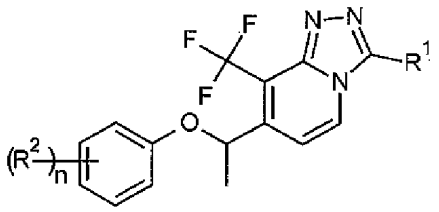
R^3 is hydrogen, fluoro, hydroxyl, hydroxyC_{1-3}alkyl, hydroxyC_{1-3}alkyloxy, fluoroC_{1-3}alkyl, fluoroC_{1-3}alkyloxy or cyano; and

Ar is unsubstituted phenyl; or phenyl substituted with n radicals R^4, wherein n is 1, 2 or 3;

R^4 is selected from the group consisting of hydrogen, halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, polyhaloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl;

or a pharmaceutically acceptable salt or a solvate thereof; and

3) a compound of Formula (I-B)



(I-B)

or a stereochemically isomeric form thereof, wherein

R^1 is selected from the group consisting of C_{1-6}alkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, and (C_{1-3}alkyloxy)C_{1-3}alkyl;

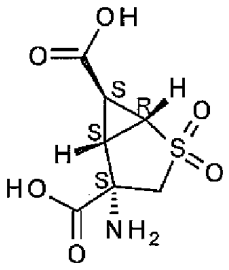
each R^2 is independently selected from F, Cl, C_{1-3}alkyl, C_{1-3}alkyloxy, mono- or polyhaloC_{1-3}alkyl, and mono- or polyhaloC_{1-3}alkyloxy;

n is an integer selected from 1, 2, and 3;

or a pharmaceutically acceptable salt or a solvate thereof; or

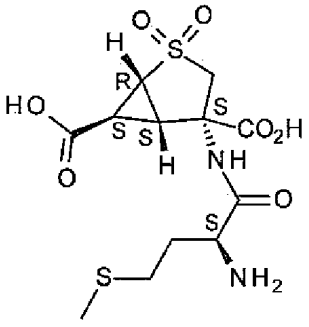
c) an orthosteric agonist of the metabotropic glutamatergic receptor subtype 2 selected from

1) LY-404039



or a salt or a solvate thereof; and

2) LY-2140023



or a salt or a solvate thereof, in particular the monohydrate thereof.

In another aspect, there is provided a pharmaceutical composition comprising a combination as defined herein, and a pharmaceutically acceptable carrier.

In another aspect, there is provided a process for the preparation of the pharmaceutical composition as defined herein, wherein the combination as defined herein is admixed with a pharmaceutical carrier.

In another aspect, there is provided a product comprising the combination of the SV2A ligand and a positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 or an orthosteric agonist of the metabotropic glutamatergic receptor subtype 2, as defined herein, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; bipolar and related disorders.

In another aspect, there is provided a combination as defined herein, or a pharmaceutical composition as defined herein, for use as a medicament.

In another aspect, there is provided a combination as defined herein, or a pharmaceutical composition as defined herein, for use in the prevention of epileptogenesis.

In another aspect, there is provided a combination as defined herein for use in the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; and bipolar and related disorders.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Dose response for the 6Hz 44mA ED_{50} determination for the Co. No. **2** and LEV alone and in combination.

Figure 2: Isobolographic analysis for the combination of Co. No. **1** with levetiracetam (LEV) in the 6Hz (44 mA) assay. Initial ED_{50} values (shown below) were determined for both Co. No. **1** and LEV (data points on x- and y-axes; filled diamonds). The theoretical line of additivity connects the calculated ED_{50} values for the two compounds (solid black line). Theoretical ED_{50} (+ SEM) for three fixed dose ratio combinations (LEV: Co. No. **1**) are plotted: 1:3 – filled squares/solid black line, 1:1 – filled upward triangles/solid black line, and 3:1 – filled downward triangles/solid black line. Experimental treatment doses were initially derived from theoretical values and adjusted according to observed effects. Experimentally-determined ED_{50} (+ SEM)

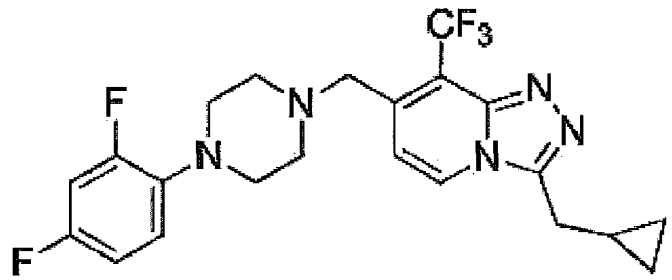
CLAIMS

1. A combination comprising

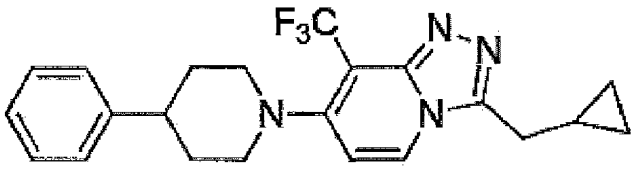
(a) a synaptic vesicle protein 2a ("SV2A") ligand selected from the group consisting of levetiracetam, brivaracetam and seletracetam; and

(b) a positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 selected from

1) a compound of Formula (I) selected from

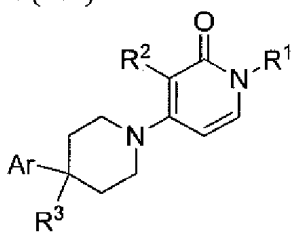


and



or a pharmaceutically acceptable salt or a solvate thereof;

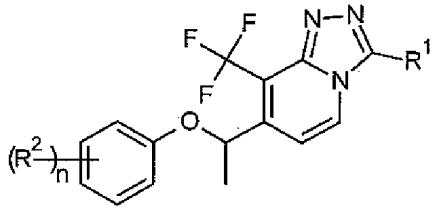
2) a compound of Formula (I-A)



(I-A)

or a stereochemically isomeric form thereof, wherein
R^1 is C_{1-6}alkyl; or C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl or trifluoromethoxy;
R^2 is halo, trifluoromethyl, C_{1-3}alkyl or cyclopropyl;
R^3 is hydrogen, fluoro, hydroxyl, hydroxyC_{1-3}alkyl, hydroxyC_{1-3}alkyloxy, fluoroC_{1-3}alkyl, fluoroC_{1-3}alkyloxy or cyano; and
Ar is unsubstituted phenyl; or phenyl substituted with n radicals R^4, wherein n is 1, 2 or 3;
R^4 is selected from the group consisting of hydrogen, halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, polyhaloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl;
or a pharmaceutically acceptable salt or a solvate thereof; and

3) a compound of Formula (I-B)



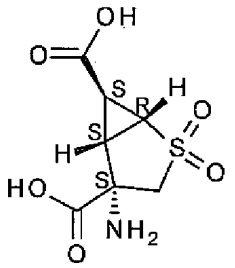
(I-B)

or a stereochemically isomeric form thereof, wherein

R^1 is selected from the group consisting of C_{1-6}alkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, and (C_{1-3}alkyloxy)C_{1-3}alkyl;
each R^2 is independently selected from F, Cl, C_{1-3}alkyl, C_{1-3}alkyloxy, mono- or polyhaloC_{1-3}alkyl, and mono- or polyhaloC_{1-3}alkyloxy;
n is an integer selected from 1, 2, and 3;
or a pharmaceutically acceptable salt or a solvate thereof; or

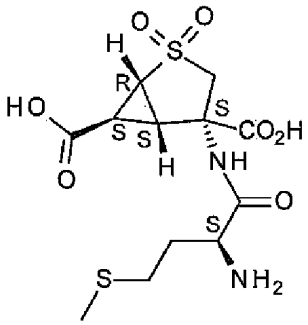
c) an orthosteric agonist of the metabotropic glutamatergic receptor subtype 2 selected from

1) LY-404039



or a salt or a solvate thereof; and

2) LY-2140023

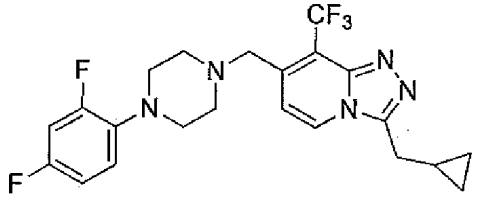


or a salt or a solvate thereof, in particular the monohydrate thereof.

2. The combination according to claim 1, wherein the SV2A ligand is levetiracetam or brivaracetam.

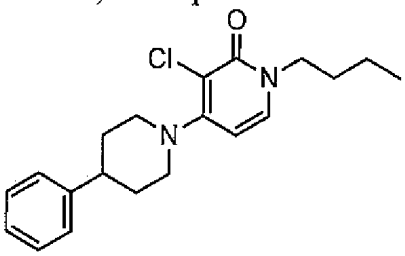
3. The combination according to claim 1 or 2, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is selected from

1) a compound of Formula (I) selected from

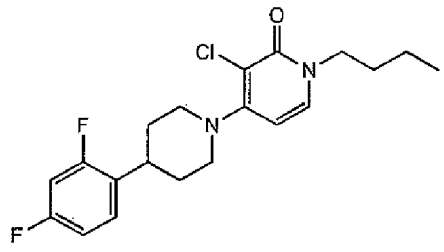


or a hydrochloride salt thereof;

2) a compound of Formula (I-A) selected from

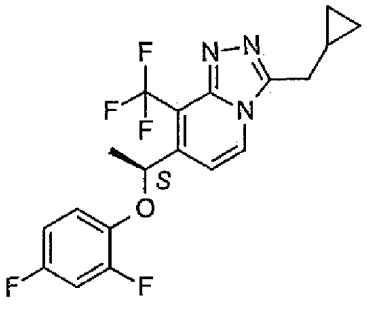


and



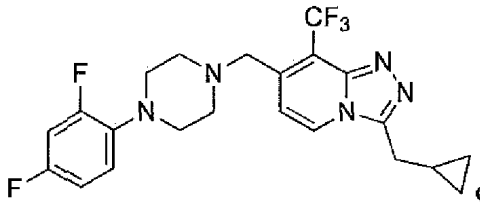
;

3) a compound of Formula (I-B) selected from



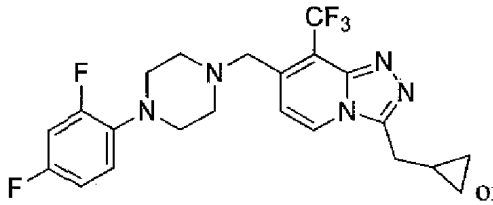
or a hydrochloride salt thereof.

4. The combination according to any one of claims 1 to 3, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is



or a hydrochloride salt thereof.

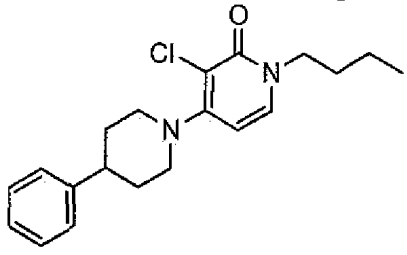
5. The combination according to any one of claims 1 to 4, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is



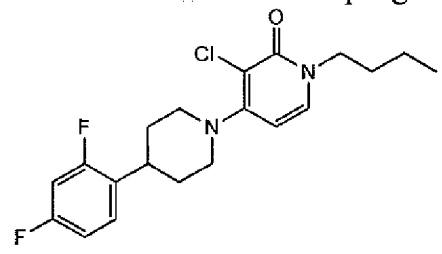
or a hydrochloride salt thereof;
and the SV2A ligand is levetiracetam.

6. The combination according to claim 5, wherein levetiracetam and the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 of Formula (I) are in a fixed-dose ratio of (a) levetiracetam : (b) compound of Formula (I) of between 1:3 to 3:1, calculated on the ED_{50} values of the individual components.

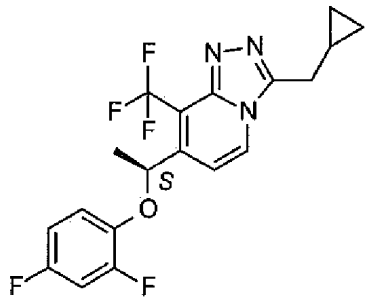
7. The combination according to any one of claims 1 to 3, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is



8. The combination according to any one of claims 1 to 3, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is



9. The combination according to any one of claims 1 to3, wherein the positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 is



or a hydrochloride salt thereof.

10. The combination according to claim 1 or 2, wherein the orthosteric agonist of the metabotropic glutamatergic receptor subtype 2 is LY-404039.

11. The combination according to claim 1 or 2, wherein the orthosteric agonist of the metabotropic glutamatergic receptor subtype 2 is LY-2140023.

12. A pharmaceutical composition comprising a combination as claimed in any one of claims 1 to 11, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 12, formulated as a combined pharmaceutical composition.

14. The pharmaceutical composition according to claim 12, formulated in separate pharmaceutical compositions.

15. A process for the preparation of the pharmaceutical composition according to claim 12 or 13, wherein the combination as claimed in any one of claims 1 to 11 is admixed with a pharmaceutical carrier.

16. A product comprising the combination of the SV2A ligand and a positive allosteric modulator of the metabotropic glutamatergic receptor subtype 2 or an orthosteric agonist of the metabotropic glutamatergic receptor subtype 2, as

defined in any one of claims 1 to 11, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; bipolar and related disorders.

17. A combination as defined in any one of claims 1 to 11, or a pharmaceutical composition as defined in any one of claims 12 to 14, for use as a medicament.

18. A combination as claimed in any one of claims 1 to 11, or a pharmaceutical composition as defined in any one of claims 12 to 14, for use in the prevention of epileptogenesis.

19. A combination as claimed in any one of claims 1 to 11 for use in the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; and bipolar and related disorders.

20. The combination for use according to claim 19, in the treatment or prevention of epilepsy and related disorders.

21. The combination for use according to claim 20, as a neuroprotectant.