that non-racemic mixtures of *R* and *S*-dimiracetam lead to activities that are superior to the activities of the single enantiomers and the racemate. This finding is the basis for the co-pending application PCT/EP2018/064125, which is incorporated herein by reference in its entirety.

Summary

It has now been surprisingly and unexpectedly found that compositions of (*R*)- and (*S*)-enantiomers of 2-(2-oxopyrrolidin-1-yl)butanamide having an enantiomeric excess (ee) of the (*S*)-enantiomer greater than or equal to 20% and lower than or equal to 67% can exhibit greater pharmacological potency, in particular in certain rat models of seizure-related disorders, than the corresponding individual enantiomers or than the racemate. These compositions of (*R*)- and (*S*)-enantiomers of 2-(2-oxopyrrolidin-1-yl)butanamide thus provide a synergistic effect that could not have been predicted based on the potency of the individual enantiomers or the racemate.

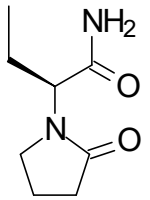
Thus, the disclosed compositions with an enantiomeric excess of (S)-2-(2-oxopyrrolidin-1-yl)butanamide are much more efficient than the corresponding racemic mixture in reducing the severity and the frequency of seizures in a model of electrical stimulation-induced seizure kindling, and in peripheral neuropathic pain in the paw-pressure test after administration of sodium monoiodoacetate or in the prevention of oxaliplatin-induced peripheral neuropathic pain or in the improvement of cognitive function.

Therefore, the disclosed compositions of (*S*)-2-(2-oxopyrrolidin-1-yl)butanamide represented by formulae (I) and and (*R*)-2-(2-oxopyrrolidin-1-yl)butanamide represented by formula (II), respectively, having an enantiomeric excess (ee) of the (*S*)-enantiomer higher than or equal to 20% and lower than or equal to 67% (preferably lower than or equal to 50%) are pharmacologically more effective at a given dose, as compared to either the pure enantiomers alone or to racemic mixtures of these compounds. The term racemic refers to a 1:1 by weight mixture of (*R*)- and (*S*)-enantiomers, which thus has an enantiomeric excess (ee) of 0%. Thus, the effect associated with the present disclosure is a synergistic effect that surprisingly results from a specific range of ratios between (S)-2-(2-oxopyrrolidin-1-yl)butanamide and (R)-2-(2-oxopyrrolidin-1-yl)butanamide represented by formulae (I) and (II), respectively.

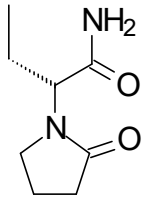
The disclosed compositions are beneficial and can be used for the treatment and/or

prevention of seizure-related disorders.

In a first example, the disclosure provides for a composition comprising a compound of formula (I) (herein also referred to as (S)-2-(2-oxopyrrolidin-1-yl)butanamide) and a compound of formula (II) (herein also referred to as (R)-2-(2-oxopyrrolidin-1-yl)butanamide)



(I)

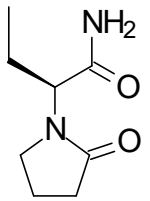


(II)

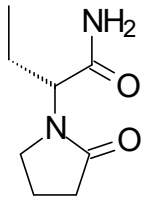
and/or pharmaceutically acceptable solvates or co-crystals thereof,

wherein the enantiomeric excess (ee) of said compound of formula (I) is equal to or higher than 20% and lower than or equal to 67% (preferably lower than or equal to 50%).

In a first aspect, the disclosure provides for a composition comprising a compound of formula (I) and a compound of formula (II)



(I)



(II)

and/or pharmaceutically acceptable solvates or co-crystals thereof,

wherein the enantiomeric excess (ee) of said compound of formula (I) is equal to or higher than 50% and lower than or equal to 67%.

In a further aspect, the disclosure provides for a pharmaceutical composition comprising the composition of the present disclosure and a pharmaceutically acceptable carrier.

In again a further example, the disclosure provides for a kit of parts comprising a compound of formula (I) and a compound of formula (II) and instructions for combining the compound of formula (I) and the compound of formula (II) to obtain an enantiomeric excess (ee) of said compound of formula (I) of equal to or higher than 20% and lower than or equal to 67% (preferably lower than or equal to 50%). In this example, the same preferred ranges of the enantiomeric excess (ee) of said compound of formula (I) and enantiomeric ratios of the compound of formula (I) to the compound of formula (II) as set out herein with respect to the composition apply.

In again a further example, the disclosure provides for the composition of the disclosure or the pharmaceutical composition of the disclosure or the kit of the disclosure for use as a medicament.

In again a further example, the disclosure provides for the composition of the disclosure or the pharmaceutical composition of the disclosure or the kit of the disclosure for the treatment and/or prevention of seizure-related disorders.

In again a further example, the disclosure provides for a method for the treatment for the treatment and/or prevention of a seizure-related disorder.

In again a further example, the disclosure provides for the use of the composition of the disclosure or the pharmaceutical composition of the disclosure or the kit of the disclosure in the manufacture of a medicament for the treatment and/or prevention of a seizure-related disorder.

In again a further example, the disclosure provides for an article of manufacture comprising the composition of the disclosure or the pharmaceutical composition of the disclosure, a container or package and a written description and administration instruction such as a package insert.

In again a further aspect, the disclosure provides for a method for preparing a composition of the disclosure or a pharmaceutical composition of the disclosure, comprising combining a compound of formula (I), and a compound of formula (II), or a compound of formula (I), and a racemate of a compound of formula (I) and (II).

In again a further aspect, the disclosure provides for a use of a compound of formula (I) and/or a compound of formula (II) and/or a racemate of a compound of formula (I) and (II) in the preparation of a composition of the disclosure or a pharmaceutical composition of the disclosure.

In again a further aspect, the disclosure provides for a use of the compound of formula (I) and the compound of formula (II) and/or pharmaceutically acceptable solvates or co-crystals thereof according to the disclosure in the manufacture of a medicament for combination therapy to treat and/or prevent a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders.

In again a further aspect, the disclosure provides for a use of the compound of formula (I) and/or pharmaceutically acceptable solvates or co-crystals thereof according to the disclosure in the manufacture of a first medicament, the compound of formula (II) and/or and pharmaceutically acceptable solvates or co-crystals thereof according to the disclosure in the manufacture of a second medicament, wherein the first and second medicaments are to be

used in combination therapy to treat and/or prevent a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders.

In again a further aspect, the disclosure provides for a use of the compound of formula (I) and/or and pharmaceutically acceptable solvates or co-crystals thereof according to the disclosure in the manufacture of a medicament for use in combinatorial therapy for treating and/or preventing a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders, and wherein said medicament is to be administered in combination with a compound of formula (II), and/or with pharmaceutically acceptable solvates or co-crystals thereof according to the disclosure.

Further aspects and examples of the present disclosure will be become apparent as this description continues.

Detailed Description

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs.

8a m "about" where used to characterize an enantiomeric excess means ±4% referring to the given numeric value, if not indicated otherwise. In each of the invention embodiments, "about" can be deleted.

The term "preferably" is used to describe features or embodiments which are not required in the present invention but may lead to improved technical effects and are thus desirable but not essential.

A number of compounds are described herein by reference to their structural formula and/or their chemical name, such as the IUPAC name. In case of discrepancies between the structural formula and the chemical name, the present invention expressly relates to the compounds as referred to by the structural formula as well as by the chemical name.

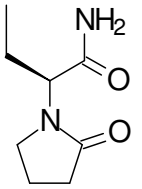
With respect to the numerical values mentioned herein, unless explicitly stated otherwise, the last decimal place of a numerical value preferably indicates its degree of accuracy. Thus, unless other error margins are given, the maximum margin is preferably ascertained by applying the rounding-off convention to the last decimal place. Thus, a value of 2.5 preferably includes the range of 2.45 to 2.54.

The term "treatment" of a disorder or disease as used herein is well known in the art. "Treatment" of a disorder or disease implies that a disorder or disease is suspected or has been

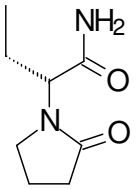
diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease). The "treatment" of a disorder or disease may, for example, lead to a halt in the progression of

CLAIMS

1. A composition comprising a compound of formula (I) and a compound of formula (II),



(I)



(II)

and/or pharmaceutically acceptable solvates or co-crystals thereof,
wherein the enantiomeric excess (ee) of said compound of formula (I) is equal to or higher than 50% and lower than or equal to 67%.

2. The composition of claim 1, wherein the
compound of formula (I) and/or pharmaceutically acceptable solvates or co-crystals thereof and
compound of formula (II) and/or pharmaceutically acceptable solvates or co-crystals thereof
are packaged separately.

3. The composition of claim 1, wherein the composition is a non-racemic mixture of 2-(2-oxopyrrolidin-1-yl)butanamide and pharmaceutically acceptable solvates or co-crystals thereof, wherein the non-racemic mixture comprises the compound of formula (I) to the compound of formula (II) in an enantiomeric excess (ee) of the compound of formula (I) of equal to or higher than 20% and lower than or equal to 67%.

4. A pharmaceutical composition comprising the composition of any one of the preceding claims and a pharmaceutically acceptable carrier.

5. The composition of any one of claims 1 to 3 or the pharmaceutical composition of claim 4 for use as a medicament.

6. The composition or the pharmaceutical composition of claim 5 for use in treating and/or preventing a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders.

7. The composition for use or the pharmaceutical composition for use of claim 6, wherein the composition or the pharmaceutical composition is to be administered orally twice daily in a dose of between 10 mg and 3000 mg per administration, more preferably between 20 mg to 2000 mg per administration, again more preferably between 50 mg and 1000 mg per administration.

8. A method for preparing a composition of any one of claims 1 to 3 or a pharmaceutical composition of claim 4, comprising combining
a compound of formula (I), and a compound of formula (II), or
a compound of formula (I), and a racemate of a compound of formula (I) and (II).

9. Use of a compound of formula (I) and/or a compound of formula (II) and/or a racemate of a compound of formula (I) and (II) in the preparation of a composition of any one of claims 1 to 3 or a pharmaceutical composition of claim 4.

10. Use of the compound of formula (I) and the compound of formula (II) and/or pharmaceutically acceptable solvates or co-crystals thereof according to any one of claims 1 to 3 in the manufacture of a medicament for combination therapy to treat and/or prevent a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders.

11. Use of the compound of formula (I) and/or pharmaceutically acceptable solvates or co-crystals thereof according to any one of claims 1 to 3 in the manufacture of a first medicament, the compound of formula (II) and/or and pharmaceutically acceptable solvates or co-crystals thereof according to any one of claims 1 to 3 in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat and/or prevent a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders.

12. Use of the compound of formula (I) and/or and pharmaceutically acceptable solvates or co-crystals thereof according to any one of claims 1 to 3 in the manufacture of a medicament for use in combinatorial therapy for treating and/or preventing a disease, injury or disorder, wherein the disease, injury or disorder is selected from seizure-related disorders, and wherein said medicament is to be administered in combination with a compound of formula (II), and/or with pharmaceutically acceptable solvates or co-crystals thereof according to any one of claims 1 to 3.