extract, raises the questions of the environmental and sustainable development as they contribute to the scarcity of fishery resources.

The glycerophospholipid vectors of omega -3 fatty acids developed are, for instance, phosphatidylserine vectors. A further one is a vector that mimics lysophosphatidylcholine for a particular family of omega-3 fatty acids including docosahexaenoic acid or DHA (WO 2018/162617). Although glycerophospholipid based vectors have a better cerebral targeting than ethyl and triglyceride form-based vectors, they have the inconvenience of being monovalent vectors of fatty acids (ex: docosahexanoic acid only), with short-term delivery only.

Thus, there is nowadays a strong need to develop new vector compounds that allow delivery of one or more active compounds, like fatty acids, in the acute (short term) and prolonged (long term) fashion, along the digestive tract, in order to provide effective treatments, not only in the cases of inflammation and epileptic seizures, but also in the preservation and/or restoration of cognitive functions associated or not with behavioral and/or psychoaffective disorders. Also, the development of fatty acid derivatives remains an important need in these applications.

SUMMARY

The inventors have developed a new family of molecular vectors and new active compounds, especially ethanolamine, ethanolamine-phosphonate or ethanolamine-phosphate derivative of saturated or unsaturated fatty acids. The active compounds have strong anti-inflammatory activity, and can decrease seizure severity and frequency and/or restore or improve cognitive functions, which may be altered in neurological disorders with a significant inflammatory component. The new family of molecular vectors includes two subfamilies, namely SphingoSynaptoLipoxins (SSLs) and AminoGlyceroPhosphoSynaptoLipoxins (AGPSLs).

In one aspect, the present disclosure relates to a compound of formula (IIA):

$$R_5\text{-NH-CH}_2\text{-CH}(R_7)\text{-PO}_3^{2-} \quad \text{(IIA)},$$

wherein:

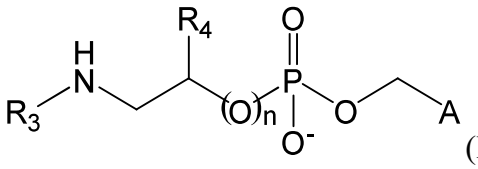
- R_5 represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms or one of its oxygen derivatives; and
- R_7 represents a hydrogen or a $(C_1\text{-}C_6)$alkyl group;

and the hydrates, or the diastereoisomers, or the pharmacologically acceptable salts thereof.

In another aspect, the present disclosure relates to a compound as disclosed herein for use as a medicine. In another aspect, the present disclosure relates to a pharmaceutical composition comprising at least one compound as disclosed herein, and an acceptable pharmaceutical excipient.

In yet another aspect, the present disclosure relates to use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for preventing and/or treating a disease chosen among an inflammatory disease or a disease associated with a cognitive disorder. In yet another aspect, the present disclosure relates to use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for preventing and/or treating a disease selected in the group consisting of epilepsy, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Crohn's Disease, Bowel's Syndrome, Dementia, and Huntington's Disease. In yet another aspect, the present disclosure relates to use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for preventing cognitive decline or restoring cognitive functions altered in brain injuries and/or in traumatic brain injuries and/or in a neuroinflammatory disease, and/or in a neurodegenerative disease.

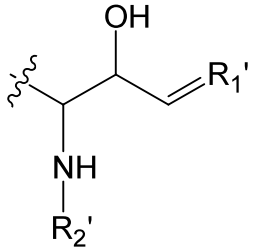
Accordingly, the present disclosure relates to a compound of formula (I):



(I),

in which:

- n is a whole number equal to 0 or 1;
- A represents a radical chosen among:
    - a group of formula (A'):

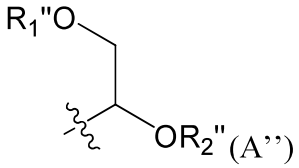


(A'),

in which:

- $R_{1'}$ represents a saturated or unsaturated (C_1-C_{24})alkyl chain optionally substituted by at least one group chosen among a hydroxyl and a halogen; and
- $R_{2'}$ represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group; or

- a group of formula (A''):



(A'')

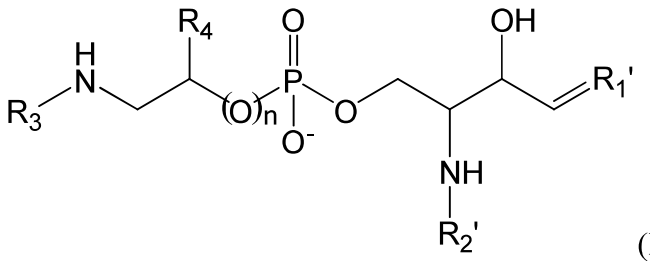
in which:

- $R_{1''}$ represents a fatty acyl, preferably saturated, comprising from 2 to 30 carbon atoms; and
- $R_{2''}$ represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group;

- R_3 represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group; and
- R_4 represents a hydrogen or a (C_1-C_6)alkyl group;

and the hydrates, or the diastereoisomers, or the pharmacologically acceptable salts thereof.

In a particular example, a compound of the disclosure has the formula (I'):



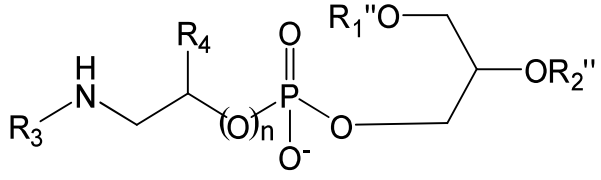
(I'),

in which:

- n is a whole number equal to 0 or 1;

- $R_{1'}$ represents a saturated or unsaturated (C_1-C_{24})alkyl chain optionally substituted by at least one group chosen among a hydroxyl and a halogen;
- $R_{2'}$ represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group;
- R_3 represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group; and
- R_4 represents a hydrogen or a (C_1-C_6)alkyl group, preferably a methyl group.

In a further particular example, a compound of the disclosure has the formula (I''):



(I''),

in which :

- n is a whole number equal to 0 or 1;
- $R_{1''}$ represents a fatty acyl, preferably saturated, comprising from 2 to 30 carbon atoms;
- $R_{2''}$ represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group;
- R_3 represents a hydrogen, a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, one of its oxygen derivatives, or a biologically active compound bound to the rest of the molecule by an acyl group; and
- R_4 represents a hydrogen or a (C_1-C_6)alkyl group, preferably a methyl group.

In a preferred example, R_3 of formulae (I), (I'), and (I") is not a hydrogen.

In a preferred example, $R_{2'}$, $R_{2''}$ and R_3 of formulae (I), (I'), and (I") are such that:

- $R_{2'}$ and $R_{2''}$ represent independently:

  - a hydrogen,

  - a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms selected in the group consisting of: acetic acid, propionic acid, butyric acid, valeric acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid,

lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linoleic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid, preferably docosahexaenoic acid, or

- an oxygen derivative of a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms chosen from resolvins, maresins, neuroprotectins and neuroprostanes ; and

- R_3 represents:

- a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms selected in the group consisting of: acetic acid, propionic acid, butyric acid, valeric acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linoleic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid, preferably docosahexaenoic acid, or

- an oxygen derivative of a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms chosen from resolvins, maresins, neuroprotectins and neuroprostanes.

The present disclosure further relates to an ethanolamine, ethanolamine-phosphonate or ethanolamine-phosphate derivative of a saturated or unsaturated fatty acid comprising from 2 to 30 carbon atoms or one of its oxygen derivatives, which can be delivered by the vectors as disclosed herein.

Accordingly, the present disclosure also relates to a compound of formula (II):

$$R_5\text{-NH-CH}_2\text{-CH}(R_7)\text{-O}_{(n)}\text{-}R_6 \text{ (II)},$$

in which:

- n is a whole number equal to 0 or 1;
- R_5 represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms or one of its oxygen derivatives; and
- R_6 is a $-PO_3^{2-}$ group;
- R_7 represents a hydrogen or a $(C_1\text{-}C_6)$alkyl group;

with the proviso that when n is equal to 1, then R_5 is not an arachidonic acid; and the hydrates, or the diastereoisomers, or the pharmacologically acceptable salts thereof.

In a preferred example, a compound of formula (II) is such that:

- n is a whole number equal to 0;

- R_5 represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, which is docosahexanoic acid; and
- R_7 represents a hydrogen.

In a further preferred example, R_5 represents:

- a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms selected in the group consisting of: acetic acid, propionic acid, butyric acid, valeric acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linoleic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid, preferably capric acid, eicosapentaenoic acid, and docosahexanoic acid, or

- an oxygen derivative of a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms chosen from resolvins, maresins, neuroprotectins, and neuroprostanes.

A further object of the disclosure is a compound of formula (I), (I'), (I'') or (II), for use as a medicine.

A further object of the disclosure is a use of a compound of formula (I), (I'), (I'') or (II) as a food supplement.

The present disclosure further relates to a pharmaceutical composition comprising at least one compound of formula (I), (I'), (I'') or (II), and an acceptable pharmaceutical excipient.

A particular example of the disclosure is a pharmaceutical composition as disclosed herein for use for preventing and/or treating a disease chosen among an inflammatory disease or a disease associated with a cognitive disorder. Preferably, the inflammatory disease is an inflammatory disease of the central nervous system, an inflammatory disease of the digestive tract, an inflammatory joint disease, or an inflammatory disease of the retina.

A further particular example of the disclosure is a pharmaceutical composition as disclosed herein for use for preventing and/or treating a disease selected in the group consisting of epilepsy, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Crohn's Disease, Bowel's Syndrome, Dementia, and Huntington's Disease.

A further particular example of the disclosure is a pharmaceutical composition as disclosed herein for use for preventing cognitive decline or restoring cognitive functions altered in brain injuries or damages, and/or in traumatic brain injuries, and/or in a neuroinflammatory disease and/or in a neurodegenerative disease.

Another object of the disclosure is a pharmaceutical composition comprising an acceptable pharmaceutical excipient and a compound of formula (II'):

$$R_{5'}\text{-NH-CH}_2\text{-CH}(R_{7'})\text{-O}_{(n)}\text{-}R_{6'} \quad \text{(II')},$$

wherein:

- n is a whole number equal to 1;
- $R_{5'}$ represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms or one of its oxygen derivatives;
- $R_{6'}$ is a hydrogen; and
- $R_{7'}$ represents a hydrogen or a $(C_1\text{-}C_6)$alkyl group; and

the hydrates, or the diastereoisomers, or the pharmacologically acceptable salts thereof;

for use for preventing and/or treating a disease associated with a cognitive or a disease selected in the group consisting of epilepsy, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Crohn's Disease, Bowel's Syndrome, Dementia, and Huntington's Disease.

Another object of the disclosure is a pharmaceutical composition comprising an acceptable pharmaceutical excipient and a compound of formula (II') as above defined, for use for preventing cognitive decline or restoring cognitive functions altered in brain injuries and/or in traumatic brain injuries and/or in a neuroinflammatory disease, and/or in a neurodegenerative disease.

In a preferred example, $R_{5'}$ represents

- a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms selected in the group consisting of: acetic acid, propionic acid, butyric acid, valeric acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linoleic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid, preferably capric acid, eicosapentaenoic acid, and docosahexanoic acid, or

- an oxygen derivative of a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms chosen from resolvins, maresins, neuroprotectins, and neuroprostanes.

According to a preferred example, the pharmaceutical compositions as disclosed herein are administered by oral route.

LEGEND OF THE FIGURES

Figure 1: General procedure for the preparation of SSL-Xs compounds

Figure 2: Separation of SSL-X1, SSL-X2 and SSL-X3 on an aminopropyl (LC-NH2) column.

Figure 3: Hydrolysis of SSL-X1 in the digestive tract.

Each animal was given *per os* 227 µg of SSL-X1 and faeces were collected after 16, 21, 26, 40, and 50 hours. A: Amount of SSL-X1 measured in the faeces at the different time points. B: administered quantities of molecule (Adm), total quantity measured in faeces at different time points (Faeces), and hydrolyzed/adsorbed quantity (hydrolyzed/adsorbed). These quantities expressed in µg of phosphorus (P) in SSL-X1 were calculated with the presumption that quantity of SSL-X1 (hydrolyzed/adsorbed) corresponds to the administered quantity minus measured quantity accumulated in the total of faeces. Results are the average ± standard deviation of 5 independent experiments.

Figure 4: Time dependent distribution of SSL-X1 along the intestinal tract of treated rats

Each animal was given *per os* 227 µg of SSL-X1. Rats were sacrificed 5 hours (panel A), 8 hours (panel B) and 36 hours (panel C) after administration of the molecule. The intestinal tract was removed and sectioned every ~ 10 cm. The content of each section is collected and the lipids extracted as described and purified. The amount of SSL-X1 in each lipid extract is determined by phosphorus determination.

Figure 5: Protocol to test the effect of synaptamide phosphonate on the expression of inflammation markers in human microglia activated by IL-1β.

Figure 6: Synaptamide phosphonate (SYN Pn) reduces the IL-1β-mediated induction of pro-inflammatory markers in immortalized human microglial cells. IHM microglial cells were treated 3 hours before exposure to IL-1β by SYN Pn at different concentrations as shown in the Figure. RNAs from inflammation markers were extracted 5 hours after IL-1β-treatment and quantified by RT-qPCR. The results are expressed as % of (IL-1β – NaCl) ± SEM (n=3).

CLAIMS

1. A compound of formula (IIA):

$$R_5\text{-NH-CH}_2\text{-CH}(R_7)\text{-PO}_3^{2-} \text{ (IIA)},$$

wherein:

- R_5 represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms or one of its oxygen derivatives; and
- R_7 represents a hydrogen or a (C_1-C_6)alkyl group;

and

the hydrates, or the diastereoisomers, or the pharmacologically acceptable salts thereof.

2. A compound according to claim 1, wherein:

- R_5 represents a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms, which is docosahexanoic acid; and
- R_7 represents a hydrogen.

3. A compound according to claim 1, wherein R_5 represents:

- a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms selected in the group consisting of: acetic acid, propionic acid, butyric acid, valeric acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, myristoleic acid, palmitoleic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linoleic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, and docosahexaenoic acid, preferably capric acid, eicosapentaenoic acid, and docosahexanoic acid, or

- an oxygen derivative of a saturated or unsaturated fatty acyl comprising from 2 to 30 carbon atoms chosen from resolvins, maresins, neuroprotectins, and neuroprostanes.

4. A compound according to any one of claims 1 to 3, for use as a medicine.

5. A pharmaceutical composition comprising at least one compound as defined in any one of claims 1 to 3, and an acceptable pharmaceutical excipient.

6. Use of a pharmaceutical composition as defined in claim 5, in the manufacture of a medicament for preventing and/or treating a disease chosen among an inflammatory disease or a disease associated with a cognitive disorder.

7. The use according to claim 6, wherein the inflammatory disease is an inflammatory disease of the central nervous system, an inflammatory disease of the digestive tract, an inflammatory joint disease, or an inflammatory disease of the retina.

8. Use of a pharmaceutical composition as defined in claim 5, in the manufacture of a medicament for preventing and/or treating a disease selected in the group consisting of epilepsy, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Crohn's Disease, Bowel's Syndrome, Dementia, and Huntington's Disease.

9. Use of a pharmaceutical composition as defined in claim 5, in the manufacture of a medicament for preventing cognitive decline or restoring cognitive functions altered in brain injuries and/or in traumatic brain injuries and/or in a neuroinflammatory disease, and/or in a neurodegenerative disease.

10. The use according to any one of claims 6 to 9, wherein said pharmaceutical composition is to be administered by oral route.