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Compounds for treatment of alzheimer's disease

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(54) Title: COMPOUNDS FOR TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: The invention relates to certain chromanol, quinone or hydroquinone compounds and derivatives thereof for treatment of Alzheimer's disease and/or for improving memory function and/or reducing plaque load. Specifically, the present invention relates to chromanol compounds chosen from (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone, ((S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride and S-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone, and pharmaceutically acceptable salts thereof.



WO 2021/118359 A1

COMPOUNDS FOR TREATMENT OF ALZHEIMER'S DISEASE

I. Field of the Invention

The invention relates to compounds for treatment of Alzheimer's disease. The
5 invention further relates to chromanol compounds and derivatives thereof for improving the
memory function.

II. Description of the Background Art

Alzheimer's disease is a progressive neurodegenerative disorder and the leading cause
10 of dementia in the elderly.

EP 2994160 B1 discloses a method for the treatment of Alzheimer's disease in
patients having moderate Alzheimer's disease and/or carrying an ApoE4 allele by
administration of pooled immunoglobulin G.

EP 2892563 B1 describes methods of treating Alzheimer's disease as adjunctive
15 therapy to acetylcholinesterase treatment comprising administering an effective daily dose of
N-(2-(6-fluoro-1H-indol-3-yl)ethyl)-3-(2,2,3,3-tetrafluoropropoxy)benzylamine or a
pharmaceutically acceptable salt to a patient in need of such treatment, wherein the effective
daily dose administered to the patient is between about 30 and about 60 mg.

EP 2937085 B1 describes that a combination of 6-[4-(1-cyclohexyl-1 H-tetrazol-5 5-
20 yl)butoxy]-3,4-dihydrocarbostyryl (cilostazol) or a salt thereof, and donepezil or a salt thereof
exhibits synergistic action for treating Alzheimer's disease.

WO2002/043666 prophetically suggests that the use of antioxidants can prevent or
reduce mental deterioration. Although antioxidants indeed may lower the oxidative burden in
mitochondria, a clear effect in treating Alzheimer is not found.

25 Cai et al. in ACS Chemical Neuroscience (2017) 8:2496-2511 describe medicaments
based on donepezil substituted with a Trolox moiety, suggested for use in the treatment of
Alzheimer. Several in vitro tests suggest some activity for some biomarkers of Alzheimer.

Amyloid beta (A β or Abeta) denotes peptides of 36–43 amino acids that are the main
component of the amyloid plaques found in the brains of people with Alzheimer's disease.
30 The peptides derive from the amyloid precursor protein (APP), which is cleaved by beta
secretase and gamma secretase to yield A β . A β molecules can aggregate to form flexible

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soluble oligomers which may exist in several forms. It is now believed that certain misfolded oligomers (known as "seeds") can induce other A β molecules to also take the misfolded oligomeric form, leading to a chain reaction resulting in plaque formation. The soluble oligomers are toxic to nerve cells, and plaques form from soluble oligomers.

5 There remains a need for new compounds for treatment of Alzheimer's disease and related diseases linked to a deterioration of the mitochondrial function and health, in particular ones that have less side effects, or preferably no side effects at all in the dosing range of such compound.

10 It is an object of the present invention to provide compounds for the treatment of Alzheimer's disease.

 It is a further object of the present invention to provide compounds for improving the memory function.

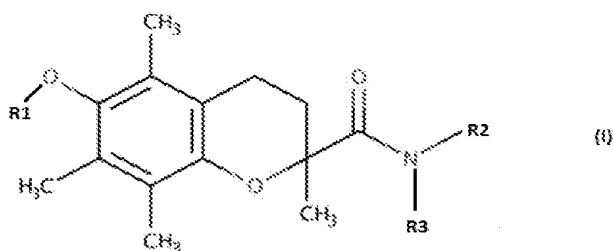
 It is a further object of the present invention to provide compounds for reducing the development of beta-plaque load in a patient that is experiencing Alzheimer disease.

15

III. Brief Summary of the invention

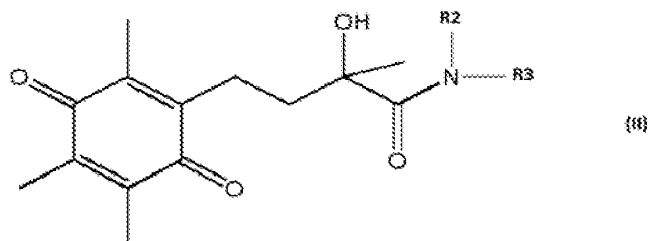
 One or more of the above objects are met by providing certain chromanol, quinone or hydroquinone compounds for one or more of said treatments.

20 The above objects are met by the present invention by providing compounds according to formula (I), (II), the hydroquinone analogue of formula (II), or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease or for improving the memory function, and/or for reducing plaque load in an Alzheimer disease patient;



25

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- wherein R1 represents a hydrogen or prodrug moiety that can be removed in living tissue
- and wherein either
 - 5 ○ R2 and R3 together with the N atom to which they are attached form a saturated or unsaturated, non-aromatic, optionally substituted, 5-8 membered ring, having one to four N, O, or S atoms, wherein R2 and R3 together contain 3-12 carbon atoms;
 - or R2 is a hydrogen atom, or an alkyl group with 1-6 carbon atoms, and R3 is
 - 10 an alkyl group, optionally substituted with nitrogen or oxygen, wherein the alkyl group comprises 3-12 carbon atoms, the alkyl group in R3 comprises one or more non-aromatic cyclic structures and may contain linear and/or branched groups, and one or more ethylenic unsaturations.

15 For the present invention, the compound according to formula (II) includes the hydrogenated quinone (i.e. the hydroquinone) analogue, although the quinone derivative is preferred in view of stability.

 In a preferred embodiment, the nitrogen can be amine, quaternary amine, guanidine or imine and oxygen is hydroxyl, carbonyl or carboxylic acid; and/or oxygen and nitrogen together may form amide, urea or carbamate groups.

20 In a preferred embodiment, R1 in formula (I) is hydrogen or forms together with the 6-oxygen an ester group with 2-6 carbon atoms.

 In a preferred embodiment of either compounds according to formula (I) or according to formula (II), R2 and R3 together with the N atom to which they are attached form a saturated ring incorporating an additional N atom, which ring is unsubstituted or substituted

25 with an alcohol, or alkanol group having 1-4 carbon atoms, such as ethylol.

 In another preferred embodiment, R2 is a hydrogen atom and R3 comprises a saturated cyclic structure having 4-7 carbon atoms and having one nitrogen atom, which ring

is unsubstituted or substituted with an alcohol, or alkanol group having 1-4 carbon atoms, such as ethylol.

According to yet another preferred embodiment, the compound is either (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone (SUL-121), ((S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (SUL-13), or (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (SUL-109).

In a most preferred embodiment, the compound is the S-enantiomer of SUL-109, namely S-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (SUL-138).

In a preferred embodiment according to the invention, the compound either according to formula (I) or according to formula (II) has a molecular weight lower than 500 Da.

As such, Trolox derivatives are described, like for example in WO2014/098586, WO2014/011047 and WO2017/060432. However, memory function or plaque formation are not investigated, nor another type of in vivo or in vitro test directly relevant for the treatment of Alzheimer disease.

WO2019/101826 suggests that some compounds comprising a Trolox moiety may act as MPGES inhibitor, which is suggested to be of advantage in treating inflammatory diseases. WO2019/101826 suggests that Alzheimer disease may act via MPGES, however, our research has not found any difference in expression in wild type-mice versus APP/PS1 mice, which indicates that MPGES is not relevant for Alzheimer disease.

Memory function and plaque formation caused by polymerization of amyloid- β are considered main issues with Alzheimer disease. Despite the fact that some antioxidants possibly reduce underlying oxidation mechanisms, no evidence has been provided that actually the memory function can be improved. The present findings show that specific Trolox derivatives can be a valuable new treatment option for treating Alzheimer Disease.

IV. Short description of the Figures

Fig. 1 shows how chronic SUL-138 treatment increases memory (Freezing %) in WT and APP mice

Fig. 2 shows how SUL-138 increases LTP maintenance in both WT and APP mice.

Fig. 3 shows that SUL-138 treatment reduces plaque numbers and size in APP/PS1 mice.

V. Detailed description of the invention

One or more of the above objects are met by the present invention by providing
5 compounds according to formula (I) or (II), as shown above, or a pharmaceutically
acceptable salt thereof for use in the treatment of Alzheimer's disease or for improving the
memory function and/or for reducing plaque load in a patient experiencing Alzheimer
disease.

Preferably, memory function is improved, while also plaque formation is reduced,
10 thereby allowing an even further improved treatment of Alzheimer Disease.

As far as improving the memory function is not considered a medical treatment, the
present invention also provides for the use of the compounds as defined for the improvement
of the memory function in a mammal. The mammal preferably is a human.

R1 can be a substituent that is easily removed in the human body, such that the
15 compound is a prodrug. R1 can be for example an amino acid derivative or ester derivative,
and generally has a molecular weight lower than 100 dalton.

In a preferred embodiment, R1 in formula (I) is hydrogen or forms together with the
6-oxygen an ester group with 2-6 carbon atoms. The ester can comprise one or more ether or
alcohol groups. Suitable esters are acetate, butyrate, 3-hydroxy butyrate and the like.

20 In a preferred embodiment of either compounds according to formula (I) or according
to formula (II), R2 and R3 together with the N atom to which they are attached form a
saturated ring having 3-6 carbon atoms and incorporating one additional N atom, which may
be substituted with 1-4 carbon atoms that may comprise an oxygen, carboxylic acid or amine
group.

25 More preferably, R2 and R3 together with the N atom to which they are attached form
a 5-7 membered ring comprising one additional amine group, which ring is optionally
substituted with methyl, ethyl, or alcohol substituted methyl or ethyl.

In another preferred embodiment, R2 is a hydrogen atom and R3 comprises a cyclic
structure having 3-6 carbon atoms and having one nitrogen atom.

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More preferably, R2 is a hydrogen atom, and R3 comprises a 5-7 membered ring comprising one additional amine group, which ring is attached to the amide-nitrogen, and which ring is optionally substituted with methyl, ethyl, or alcohol substituted methyl or ethyl.

In either case, the ring (the cyclic structure formed by R2 and R3, or of R3 alone) may
5 be unsubstituted or substituted with an alkyl having 1-4 carbon atoms, alcohol, or alkanol group having 1-4 carbon atoms, such as ethylol.

In a preferred embodiment according to the invention, the compound either according to formula (I) or according to formula (II) has a molecular weight lower than 500 Da.

Certain chromanol compounds have been described in WO2014/098586. The
10 compounds described in detail have abbreviations, referring to SUL-XXX (XXX being a 2 or 3 digit number). Many of these compounds are racemic mixtures, although some enantiomers have been tested as well. Suitable methods to prepare chromanol compounds according to the present invention are described in WO2014/098586 or WO2014/011047.

WO 2017060432 A1 discloses amide-derivatives of 2-hydroxy-2-methyl-4-(3,5,6-
15 trimethyl-1,4-benzoquinon-2-yl)-butanoic acid and methods of making such compounds.

Hydrogenated quinone derivatives can be easily prepared by hydrogenation of the quinone structure.

According to yet another preferred embodiment, the compound is either (6-hydroxy-
2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone (SUL-121), ((S)-6-hydroxy-
20 2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (SUL-13), or (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (SUL-109).

In a most preferred embodiment, the compound is the S-enantiomer of SUL-109,
namely S-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-
25 yl)methanone (SUL-138).

The counterion in the pharmaceutically acceptable salt can be a counterion as known in the art. Preferably, the compounds have at least one basic nitrogen, an amine, which can be protonated. The counterion preferably is a halogen such as chloride, sulphate, citrate, formate or the like, and most preferably chloride.

The compounds are effective as a racemic mixture or in a substantially pure
30 enantiomeric form. The compounds have one or more chiral centers, generally one or two.

Preferably, the compound is a substantially enantiomerically pure compound. Substantially enantiomerically pure is about 95% enantiomeric excess or more, more preferably about 98% enantiomeric excess, and most preferably about 99% or more enantiomeric excess. Also, in case the compound contains more than one chiral center, these amounts apply.

The compounds are preferably used in effective amounts, to achieve an improvement in memory function and/or to achieve treatment of Alzheimer's disease.

The term 'treatment' encompasses reduction in progress of the disease and/or improvement in symptoms of the disease.

Effects generally are observed with amounts of about 1 μM in body fluid, but preferably higher amounts are used. Preferred amounts are concentrations in vivo or in vitro of about 10 μM or higher, more preferably about 20 μM or higher. Generally, a concentration in human of about 200 μM or lower should be sufficient and safe.

For human use, this would mean – assuming a 30 L distribution volume, 100% availability and a concentration of about 1 μM – a dosage of about 10 mg or more. Preferred amounts would result in a concentration of about 10 μM – for which a dosage of about 100 mg or more would be suitable. Hence, preferably, dosage forms of about 20 mg or more, preferably 50 mg or more, preferably 100 mg or more are suitable. Generally, solid, oral dosage forms contain as a maximum about 500 mg compound, preferably about 450 mg or less, to allow for excipients. With i.v. other liquid forms of administration, larger amounts can be administered.

Examples of dosages which can be used are an effective amount of the compounds of the invention of a dosage of 0.2 mg/kg or higher, such as preferably within the range of about 1 mg /kg to about 100 mg/kg, or within about 2 mg /kg to about 40 mg/kg body weight, or within about 3 mg/kg to about 30 mg/kg body weight, or within about 4 mg/kg to about 15mg/kg body weight. Compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided dosage of two, three or four times daily.

The compounds described herein can be formulated as pharmaceutical compositions by formulation with additives such as pharmaceutically or physiologically acceptable excipients carriers, and vehicles.

Suitable pharmaceutically or physiologically acceptable excipients, carriers and vehicles include processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl- β -cyclodextrin, polyvinylpyrrolidone, low melting waxes, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences, " Mack Pub. Co. , New Jersey (1991).

A pharmaceutical composition preferably comprises a unit dose formulation, where the unit dose is a dose sufficient to have a therapeutic effect. The unit dose may be a dose administered periodically in a course of treatment or suppression of a disorder.

In addition, the unit dose may be a dose administered periodically in a course of treatment to improve native cognitive functions related to memory.

The compounds of the invention may be administered enterally, orally, parenterally, sublingually, by inhalation (e. g. as mists or sprays), rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically or physiologically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intratarsal injection, or infusion techniques. The compounds are mixed with pharmaceutically acceptable carriers, adjuvants, and vehicles appropriate for the desired route of administration.

Oral administration is a preferred route of administration, and formulations suitable for oral administration are preferred formulations.

The compounds described for use herein can be administered in solid form, in liquid form, in aerosol form, or in the form of tablets, pills, powder mixtures, capsules, granules, injectables, creams, solutions, suppositories, enemas, colonic irrigations, emulsions, dispersions, food premixes, and in other suitable forms. The compounds can also be administered in liposome formulations.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for

example, as a solution in propylene glycol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at room temperature but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavouring, and perfuming agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host to which the active ingredient is administered and the particular mode of administration. The unit dosage chosen is usually fabricated and administered to provide a defined final concentration of drug in the blood, tissues, organs, or other targeted region of the body. The effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician or skilled person.

The present invention will be further illustrated using the examples below. In the examples, reference is made to figures.

VI. Examples

Example 1

5 The effectiveness of the compounds according to the invention for treatment of Alzheimer's disease was tested by two independent tests: one reflecting memory and one showing synaptic connectivity.

Methods and Experimental Details

10 The APP/PS1 mouse model is a widely used A-beta pathology model for Alzheimer's disease (AD) (1 of the 2 main neuropathological hallmarks of AD). These mice contain human transgenes for APP (Swedish mutation) and PSEN1 (L166P mutation), which will lead to pathological amyloid deposition in the brain and impairments in hippocampal dependent memory and Long Term Potentiation (LTP) starting at ~3 months of age (3 moa).

15 The effectiveness of SUL-138 ((6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone) in relieving/preventing common pathology in the APP/PS1 model was tested. The effect on memory was tested in a hippocampal dependent context test (Fear conditioning (FC)) and synaptic connectivity was tested via electrophysiological LTP (Long-term potentiation) measurements. Both are impaired in this mouse model under basal conditions. In addition, Phenotypers (Sylics) were used to exclude
20 that SUL-138 induces atypical behavior after chronic oral treatment.

25 Wild type (WT) and APP/PS1 mice were each divided in 2 groups, either receiving vehicle or SUL-138 via their food. Group size amounted 12 animals. Based on mouse weight of ~30g, food intake of ~5g/day and desired oral intake of 30 mg/day/kg, food pellets were sprayed with SUL-138 in water with 0.0145 % ethanol at 1g SUL-138 in 5kg food. Vehicle
30 food was prepared by spraying with the same volume of 0.0145 % ethanol containing water.

 Mice were treated chronically between 2.5 moa (pre-pathology/memory deficit) and 6 moa (age at which clear neuropathology and memory deficits occur) prior to testing.

 FC: mice were exposed to a context for 2 min after which they received a 0.7 mA footshock. 30 sec after the footshock mice were out back in home cage. 24h later mice were
30 put in the same context and freezing levels were measured for 2 min.

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LTP: Acute coronal hippocampal slices were kept in artificial CSF and LTP was measured after 3x 100 Hz stimulation.

Phenotypers (provided by Sylics, Amsterdam, Netherlands): Mice were housed in the phenotypers for 3 days during which spontaneous behavior: activity, dark/light, habituation, kinematics, light dark phase transition pattern and sheltering were measured.

Results

Overall welfare was monitored and did not show differences between vehicle and SUL-138 treated animals, with all groups showing similar increase in body weight.

Memory was assessed at 6 moa by measuring freezing following context acquisition.

Fig. 1 shows how chronic SUL-138 treatment increases memory (Freezing %) in WT and APP mice. SUL-138 treatment increased freezing levels (memory) in both the WT and APP mice. Student's t-test, *: $p < 0.05$ **: $p < 0.01$.

APP/PS1 mice showed decreased freezing compared to WT mice when treated with control food, as expected. Upon chronic SUL-138 treatment memory in APP/PS1 mice was restored to WT levels. This shows that SUL-138 is effective in preventing or ameliorating Alzheimer's disease and/or its symptoms.

Interestingly, WT mice that received SUL-138 also performed better in the memory task. This indicates that SUL-138 is also effective for improving the memory function in a healthy mammal.

Fig. 2 shows how SUL-138 increases LTP maintenance in both WT and APP mice. Between 8-14 hippocampal slices per group (2A: WT ctrl, WT SUL-138, 2B: APP ctrl, APP SUL-138) received LTP evoked by 3x 100 Hz stimulation (tetanus) of 1 sec separated by 20 sec. The slope was measured for 60 min. LTP was expressed as a percentage of baseline. All LTP data analysis was performed blinded. LTP maintenance (min 30-60) was significantly ($p < 0.05$) higher in SUL-138 animals (both WT and APP); Student's t-test, * $P < 0.05$; 2C.

Chronic SUL-138 treatment did not induce differences in spontaneous behavior: activity, dark/light, habituation, kinematics, light dark phase transition pattern and sheltering were measured.

Conclusions

The examples show SUL-138 to increase memory and LTP in both WT and APP/PS1 mice, and to effectively restore in APP/PS1 mice memory and LTP to control levels.

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Increase in both these parameters reflects a general plasticity increasing/LTP facilitating process which is stimulated using SUL-138. This finding implies that SUL-138 may be used to relieve symptoms in neurological diseases that display reduced synaptic strength or plasticity.

5 SUL-138 effects seem specific for memory improvement, as treatment did not introduce atypical behavior in mice after chronic treatment for 3 m. In addition, no differences in weight were measured during 3 m of chronic oral treatment, that could indicate aversive or addictive behavior towards SUL-138-treated food, or changes in major physiological functions.

10 Finally, no animal welfare problems or differences between groups took place during the total experiment.

Example 2

Reduced Plaque load in APP/PS1 mice after intervention by SUL-138

15

APP/PS1 (n=10) and wildtype mice (WT, n = 10) mice were treated, either with vehicle or SUL-138. Mice were treated for 3 months starting at 3 months of age with either SUL-138 or vehicle treated food pellets. The mice were sacrificed at 6 months of age, the age at which (among others) hippocampal dependent memory impairment and apparent plaque load are expected.

20

4% PFA perfused brains, stored on sucrose, were sliced at 35 μ M using a cryostat (-20 °C; Leica). Hippocampal slices (n=2/animal; 5 animals/group) were washed 3x 10 min with 1x PBS, and then blocked for 1h in Blocking solution (10mL 1x PBS + 500 μ L normal Goat Serum + 0.250 g Bovine Serum Albumin + 20 μ L Triton-100). The slices were

25 incubated overnight with anti-Amyloid beta (6E10) (ITK Diagnostics, 1:400), washed 3x 10 min with 1x PBS and then incubated with secondary Goat anti-mouse Alexa fluorescent 488 antibody (Sigma-Aldrich, 1:250) for 2h. Then slices were washed 3x 10 min with 1x PBS and mounted on slides.

30

Slices were imaged using the Zeiss Cell Discover 7 high content microscope with LSM900 confocal head. Using Fiji, both hippocampi were selected separately for 5 animals per group (yellow line in Figure 3A) and number and size of plaques were measured (Figure

3B, C). The mean number of plaques and plaque size per animal were used for statistical analyses in GraphPad 8 using Student's *t*-test, one-sided.

Three months of oral SUL-138 reduced both the number of plaques (Figure 3B; $p = 0.0138$) and plaque size (Figure 3C; $p = 0.0021$) in APP/PS1 mice compared to vehicle treated mice. SUL-138 and vehicle treated WT animals did not show any plaques.

These data, together with SUL-138 rescuing memory and increasing synaptic transmission (long-term potentiation) in APP/PS1 mice observed according to example 1, show that SUL-138 is a potential therapeutic option against Alzheimer disease.

The bioavailability of SUL-138 brain appears to be high, thereby overcoming problems of other mitochondrial targeted compounds, making it a more suitable treatment option for future clinical application.

Example 3

In vitro assays showing that compounds according the present invention are active.

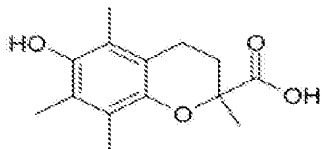
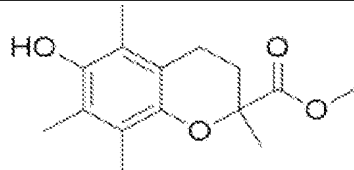
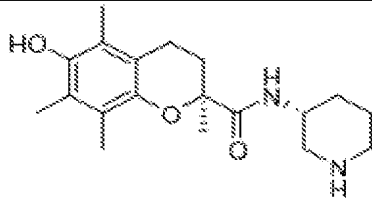
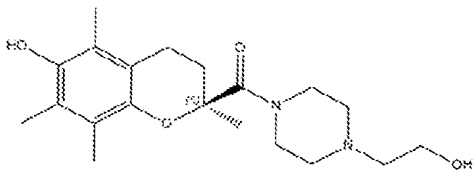
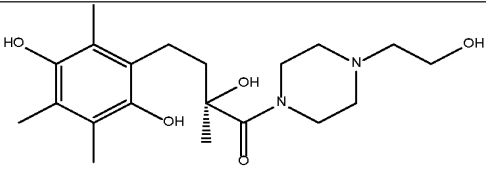
Excitotoxicity is the process wherein nerve cells suffer damage or death when the levels of otherwise necessary and safe neurotransmitters become pathologically high, resulting in the excessive stimulation of their receptors. Excitotoxicity may be involved in neurodegenerative diseases of the central nervous system such as Alzheimer's disease.

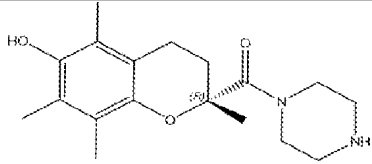
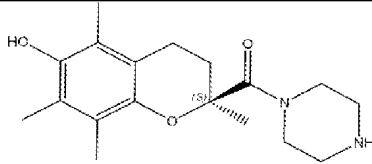
In vitro assays to investigate excitotoxicity utilize well-characterized inducers of neuronal cell death (*e.g.* glutamate, dopamine or NDMA) and the quantification of cell viability of stimulated neuronal-like cells. The human neuroblastoma-derived SH-SY5Y cell line can be differentiated *in vitro* to resemble mature neurons morphologically and biochemically. Moreover, the differentiated SH-SY5Y neuron-like cells are sensitive to excitotoxicity induced by, amongst others, glutamate and dopamine.

In this current study, the efficacy of SUL-11, SUL-127, SUL-13, SUL-138 (and its primary metabolite SUL-138M2), SUL-150 and SUL-151 to inhibit glutamate- and dopamine-induced excitotoxicity of human SH-SY5Y neuronal-like cells were investigated. SUL-11 is Trolox, while SUL-127 is the methyl ester of Trolox. These two compounds were used as reference.

The compounds used in this study are shown in Table 1, below:

Table 1

Compound	Chemical Name	Formula	Structure	MW
Reference compounds				
SUL-11	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid	C ₁₄ H ₁₈ O ₄		250.3
SUL-127	methyl 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-carboxylate	C ₁₅ H ₂₀ O ₄		264.3
compounds according the invention				
SUL-13	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chromane-2-carboxamide	C ₁₉ H ₂₈ N ₂ O ₃		332.4
SUL-138	(S)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone	C ₂₀ H ₃₀ N ₂ O ₄		362.5
SUL-138M2	4-(2,5-dihydroxy-3,4,6-trimethylphenyl)-2-hydroxy-1-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylbutan-1-one	C ₂₀ H ₃₂ N ₂ O ₅		380.5

Compound	Chemical Name	Formula	Structure	MW
SUL-150	(R)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone	C ₁₈ H ₂₆ N ₂ O ₃		318.4
SUL-151	(S)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone	C ₁₈ H ₂₆ N ₂ O ₃		318.4

Human SH-SY5Y neuroblastoma cells (ATCC #CRL-2266) were maintained in DMEM medium containing 10% fetal bovine serum and 1% Penicillin-Streptomycin solution (#P4333, Sigma-Aldrich, St. Louis, MO) and passaged when the cultures reach a confluency of 70%. Prior to experiments, SH-SY5Y cells were differentiated by serum reduction (to 1%) and stimulation with 10 μ M retinoic acid (#R7882, Sigma-Aldrich, St. Louis, MO) for 72 hours. Differentiated SH-SY5Y cells were seeded at $0.6 \cdot 10^5$ cells/cm² for all experiments.

Differentiated SH-SY5Y cells were pre-incubated with SUL compounds (dose range $8 \cdot 10^{-4}$ to $1 \cdot 10^{-8}$ M) under standard culture conditions for 30 min and then stimulated with either l-glutamate (60 mM; #12843-0, Sigma-Aldrich, St. Louis, MO) or dopamine (100 μ M; #H8502, Sigma, St. Louis, MO) for an additional 24 h. Neutral Red Assay Solution (#N2889, Sigma-Aldrich, St. Louis, MO) was added to the cultures at a 10% (v/v) concentration during the final 4 hours of culture. Cells were washed with warm PBS and Neutral red solubilized in acid ethanol (1% acetic acid in 50% EtOH). Absorbances were recorded at 540 nm in a CLARIOStar Plus plate reader (BMG Labtech, Germany). Cell viability was normalized to absorbance measurements of untreated cultures (100% viable) and to absorbance measurements of samples that did not contain cells (0% viable).

All experiments were performed in triplicate per condition and averaged. Data obtained from two individual experiments were used for evaluation in GraphPad Prism 8.0 (GraphPad Software Inc, Ca). 4 parameter non-linear regression was used to determine the efficacy and potency of SUL compounds to reduce the excitotoxicity induced by either l-glutamate or dopamine. The efficacy of SUL compounds to inhibit excitotoxicity was

calculated as $E_{\max} = 100 \cdot (V_{(\text{treated})} - V_{(\text{vehicle})}) / (100\% - V_{(\text{vehicle})})$, wherein V is the observed viability and E_{\max} is the maximal effect evoked by SUL compound treatment.

No cellular toxicity was observed as a decrease in viability when using the SUL-compounds in the molar range shown in the table below.

5 SH-SY5Y neuroblastoma cells were differentiated into neuronal-like cells according to established protocols and stimulated with 60 mM glutamate to induce excitotoxicity. Glutamate decreased SH-SY5Y cell viability from $100 \pm 1.63\%$ in vehicle-treated control cells to $55.4 \pm 1.7\%$ in SH-SY5Y cells exposed to glutamate for 24 hours ($p < 0.0001$). Pre-incubation of differentiated SH-SY5Y cells with SUL compounds (10^{-3} to 10^{-8} M) dose-
10 dependently increased cell viability of glutamate-challenged SH-SY5Y cells, albeit at different levels. Trolox and the methyl-ester of Trolox were clearly less effective than the other SUL-compounds, as shown in table 2 below.

Differentiated SH-SY5Y neuroblastoma cells were stimulated with 150 μ M dopamine to induce excitotoxicity. Dopamine decreased SH-SY5Y cell viability from $100 \pm 0.8\%$ in
15 vehicle-treated control cells to $50.5 \pm 1.0\%$ in SH-SY5Y cells exposed to dopamine for 24 hours ($p < 0.0001$). Pre-incubation of differentiated SH-SY5Y cells with SUL compounds (10^{-3} to 10^{-8} M) dose-dependently increased cell viability of dopamine-challenged SH-SY5Y cells, albeit at different efficacies, as shown in table 2 below. In this model, all compounds had decreased cell viability at the dose level of 10^{-3} M.

20

Table 2:

Compound	Glutamate excitotoxicity		Dopamine excitotoxicity	
	EC ₅₀ (M)	E _{max} (%)	EC ₅₀ (M)	E _{max} (%)
SUL-11	$4.62 \cdot 10^{-6}$	76,7	$8.35 \cdot 10^{-6}$	79,5
SUL-127	$2.01 \cdot 10^{-5}$	90,4	$3.53 \cdot 10^{-6}$	69,5
SUL-13	$3.82 \cdot 10^{-6}$	100,0	$3.24 \cdot 10^{-7}$	91,9
SUL-138	$1.42 \cdot 10^{-6}$	100,0	$6.60 \cdot 10^{-7}$	100,0
SUL-138M2	$4.43 \cdot 10^{-6}$	100,0	$1.69 \cdot 10^{-6}$	94,7
SUL-150	$1.22 \cdot 10^{-7}$	100,0	$5.55 \cdot 10^{-8}$	100,0
SUL-151	$9.61 \cdot 10^{-8}$	100,0	$6.92 \cdot 10^{-8}$	100,0

The results in the table show that the SUL compounds according to the present invention exhibit either an improved EC50 (i.e. active at lower concentration), and/or improved Emax (i.e. the restoration of the toxicity is achieved at a higher level). Thereby, this example shown
5 that next to SUL-138, also other SUL-compounds as claimed are likely to show the advantages of improved memory function and/or reduced plaque formation; i.e. in general are favorable in treating Alzheimer disease.

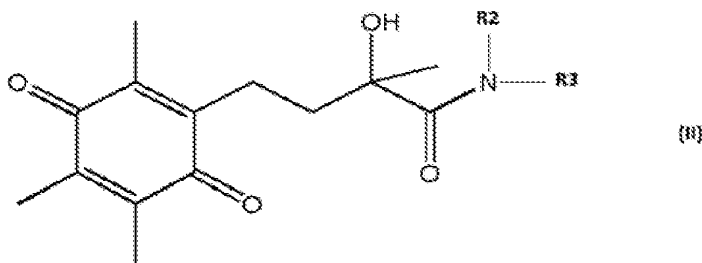
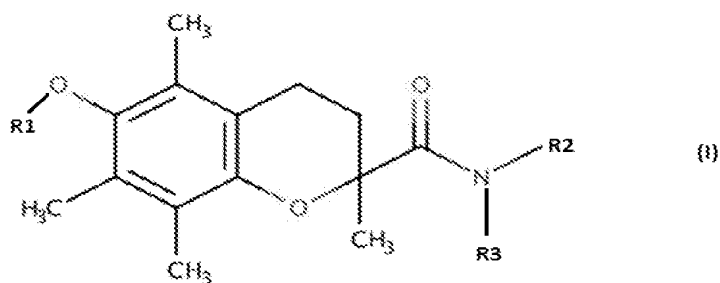
Reference experiment A

10 Hippocampal tissue from wildtype and APP/PS1 mice was examined for the protein expression of prostaglandin synthases and the thromboxane synthase A. Peptides resembling the prostaglandin synthase PTGS1, PTGES2, PTGES3, and PTGFS were found in the hippocampal tissue of both wildtype and APP/PS1 mice (Table 4). No protein fragments of
15 PTGS2, PTGDS, PTGES1, PTGIS and TXA could be found. SUL-138 treatment of either wildtype or APP/PS1 mice did not alter the protein expression of prostaglandin synthesizing enzymes.

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Claims

1. Compound according to formula (I) or (II), or a pharmaceutically acceptable salt thereof for use in the treatment of Alzheimer's disease, for improving the memory function, and/or for reducing plaque load in an Alzheimer disease patient;



- wherein R1 represents a hydrogen or prodrug moiety that can be removed in living tissue
- and wherein either

- 10 ○ R2 and R3 together with the N atom to which they are attached form a saturated or unsaturated, non-aromatic, optionally substituted 5-8 membered ring, having one to four N, O, or S atoms, wherein R2 and R3 together contain 3-12 carbon atoms;
- 15 ○ or R2 is a hydrogen atom, or an alkyl group with 1-6 carbon atoms, and R3 is an alkyl group, optionally substituted with nitrogen or oxygen, wherein the alkyl group comprises 3-12 carbon atoms, the alkyl group in R3 comprises one or more non-aromatic cyclic structures and may contain linear and/or branched groups, and one or more ethylenic unsaturations.

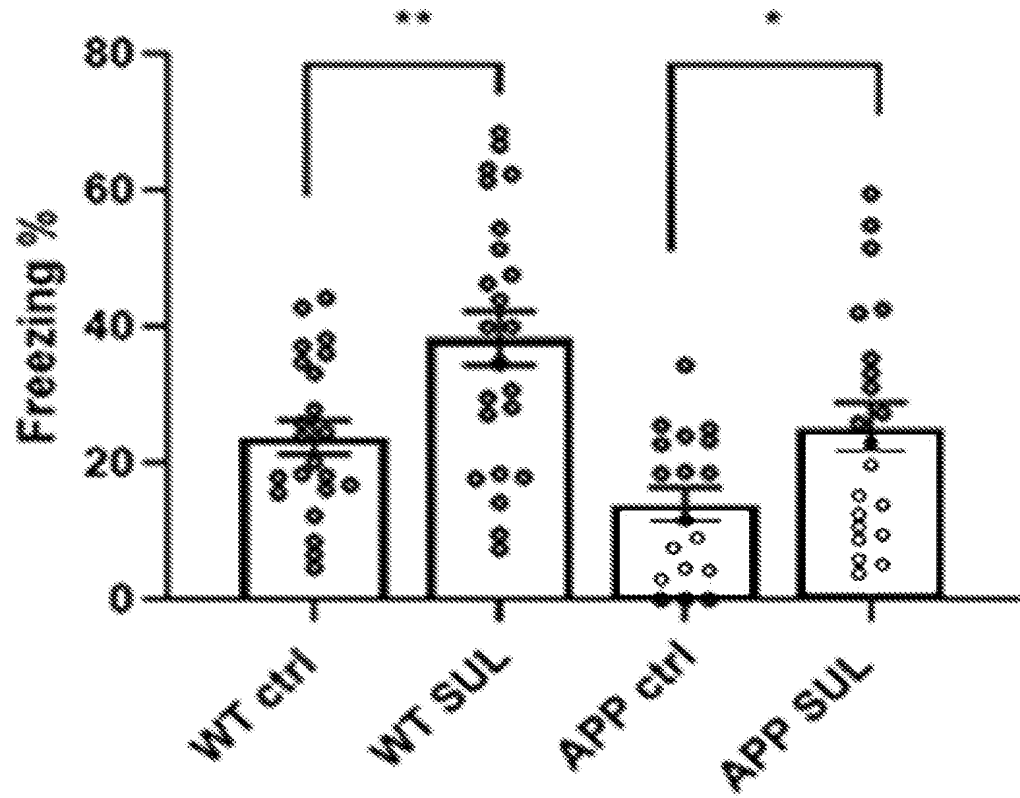
-19-

2. Compound for use according to claim 1, wherein R1 is hydrogen or forms together with the 6-oxygen an ester group with 2 - 6 carbon atoms.
3. Compound for use according to any one of claims 1-2, wherein the nitrogen can be
5 amine, quaternary amine, guanidine, or imine and oxygen is hydroxyl, carbonyl or carboxylic acid; and/or oxygen and nitrogen together form amide, urea or carbamate groups.
4. Compound for use according to any one of claims 1-3, wherein in either compounds
10 according to formula (I) or according to formula (II), R2 and R3 together with the N atom to which they are attached form a saturated ring incorporating an additional N atom, which ring is unsubstituted or substituted with an alcohol, or alkanol group having 1-4 carbon atoms.
- 15 5. Compound for use according to claim 4, wherein the compound is a compound according to formula I.
6. Compound for use according to claim 5, wherein R2 and R3 together with the N atom
20 to which they are attached form a 5-7 membered ring comprising one additional amine group, which ring is optionally substituted with methyl, ethyl, or alcohol substituted methyl or ethyl.
7. Compound for use according to any one of claims 1-3, wherein R2 is a hydrogen atom
25 and R3 comprises a saturated cyclic structure having 4-7 carbon atoms and having one nitrogen atom, which ring may be substituted with an alkyl group, alcohol group, or with a group with 1-4 carbon atoms that may comprise an oxygen, carboxylic acid or amine group.
8. Compound for use according to claim 7, wherein the compound is a compound
30 according to formula II and wherein R2 is a hydrogen atom and R3 comprises a cyclic structure having 4-6 carbon atoms and having one nitrogen atom which ring is optionally substituted with methyl, ethyl, or alcohol substituted methyl or ethyl.

9. Compound for use according to claim 1, wherein the compound is (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(piperazin-1-yl)methanone (SUL-121), ((S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (SUL-13) or (6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (SUL-109).
- 5
10. Compound for use according to claim 9, wherein the compound is the S-enantiomer of SUL-109: S-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (SUL-138).
- 10
11. Compound for use according to any of claims 1-8, wherein the compound according formula (I) or formula (II) has a molecular weight lower than 500 Da.
- 15
12. Compound for use according to any of the preceding claims, wherein the use is for treating Alzheimer's disease.
13. Compound for use according to any of claims 1-12, wherein the use is for improving memory function.
- 20
14. Compound for use according to any of claims 1-13, wherein the use is for reducing plaque load in an Alzheimer disease patient.
15. Use of a compound as described in any one of claims 1-11 for improving the memory function in a mammal, preferably a human.
- 25

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Figure 1



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Figure 2

Minutes: 30-60

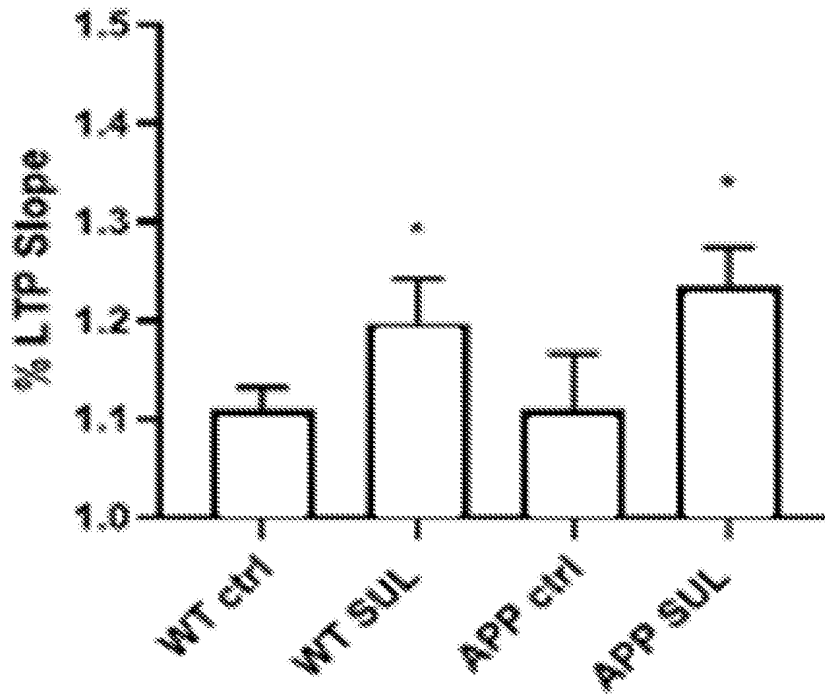
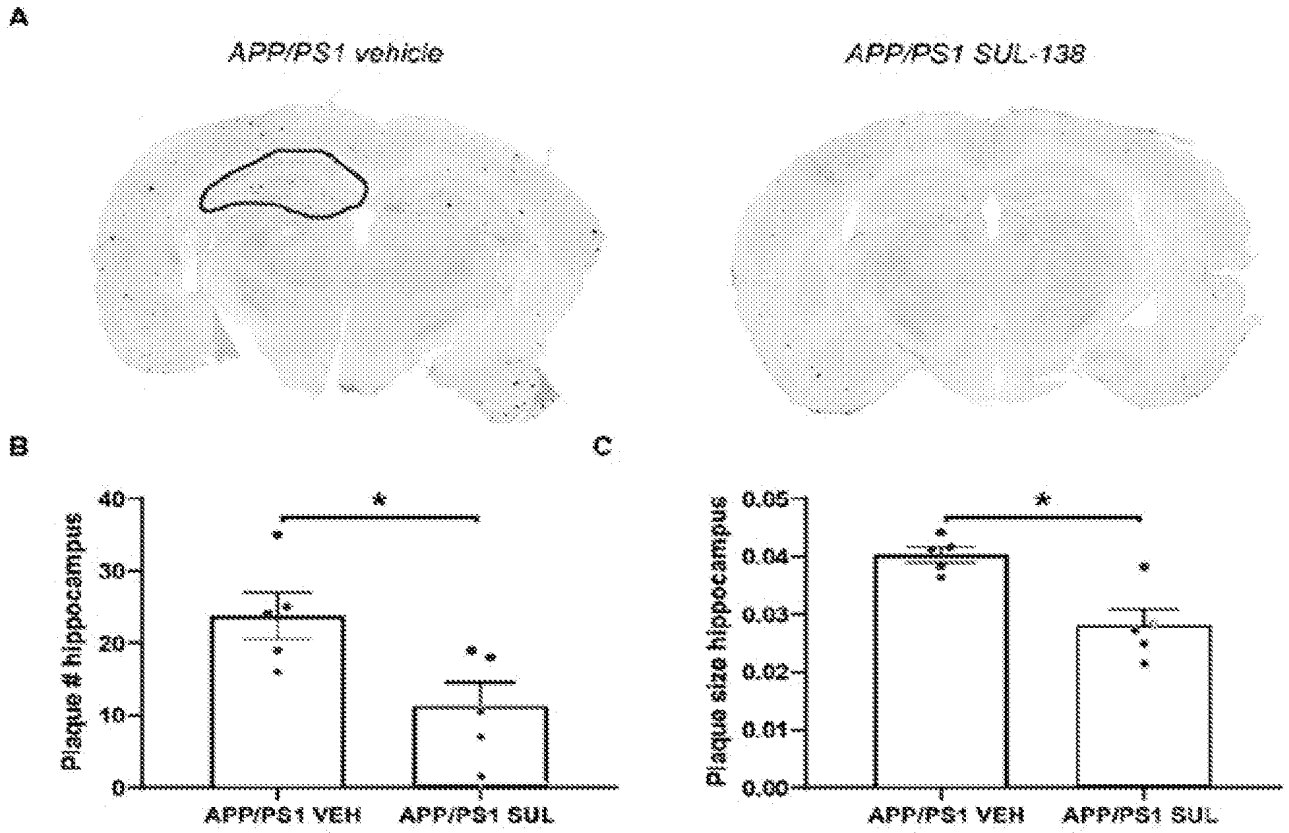


Figure 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2020/050782

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/453 A61K31/496 A61P25/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2014/098586 A1 (SULFATEQ B V [NL]) 26 June 2014 (2014-06-26) page 9; claim 3 pages 11-12; table 1 -----	1-6, 9-12, 15 1-15
X Y	WO 2014/011047 A1 (KHONDRION B V [NL]) 16 January 2014 (2014-01-16) claim 10; examples -----	1-7, 9, 11, 12, 15 1-15
X Y	WO 2017/060432 A1 (KHONDRION IP B V [NL]) 13 April 2017 (2017-04-13) pages 56-57; claim 12; examples -----	1-9, 11, 12, 15 1-15
X Y	WO 2019/101826 A1 (KHONDRION IP B V [NL]) 31 May 2019 (2019-05-31) claim 6; examples -----	1-9, 11, 12, 15 1-15
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 4 March 2021	Date of mailing of the international search report 15/03/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Loher, Florian
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INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2020/050782

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2009/061744 A2 (EDISON PHARMACEUTICALS INC [US]; JANKOWSKI ORION D [US] ET AL.) 14 May 2009 (2009-05-14) claims 13, 16 -----	1-4,7,8, 11,12,15 1-15
Y	PEI CAI ET AL: "Rational Design and Multibiological Profiling of Novel Donepezil-Trolox Hybrids against Alzheimer's Disease, with Cholinergic, Antioxidant, Neuroprotective, and Cognition Enhancing Properties", ACS CHEMICAL NEUROSCIENCE, vol. 8, no. 11, 25 August 2017 (2017-08-25), pages 2496-2511, XP055705017, US ISSN: 1948-7193, DOI: 10.1021/acschemneuro.7b00257 abstract -----	1-15
Y	WO 02/43666 A2 (COLGATE PALMOLIVE CO [US]) 6 June 2002 (2002-06-06) claim 10 -----	1-15
X	SUNG SYUAN ET AL: "Early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease.", FASEB JOURNAL, vol. 18, no. 2, 4 December 2003 (2003-12-04), pages 323-325, XP055781871, ISSN: 0892-6638, DOI: 10.1096/fj.03-0961fje -----	1-12,14
Y	page 2, paragraph 3 page 4, last paragraph page 5, paragraph 3 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2020/050782

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 2014098586	A1	26-06-2014	AU 2013364538 A1	09-07-2015
			CA 2895701 A1	26-06-2014
			CY 1120682 T1	11-12-2019
			DK 2935232 T3	17-09-2018
			EP 2935232 A1	28-10-2015
			EP 3388426 A2	17-10-2018
			ES 2686599 T3	18-10-2018
			HR P20181434 T1	19-10-2018
			HU E039373 T2	28-12-2018
			JP 6359558 B2	18-07-2018
			JP 6684861 B2	22-04-2020
			JP 2016511743 A	21-04-2016
			JP 2018162280 A	18-10-2018
			LT 2935232 T	25-09-2018
			MX 371337 B	27-01-2020
			NL 2010010 C2	23-06-2014
			PL 2935232 T3	31-12-2018
			PT 2935232 T	11-10-2018
			SI 2935232 T1	30-10-2018
			US 2015342174 A1	03-12-2015
			US 2019098890 A1	04-04-2019
			WO 2014098586 A1	26-06-2014
			ZA 201504602 B	26-07-2017

WO 2014011047	A1	16-01-2014	AU 2013287347 A1	22-01-2015
			CA 2878567 A1	16-01-2014
			CN 104662011 A	27-05-2015
			DK 2872497 T3	24-04-2017
			EP 2872497 A1	20-05-2015
			ES 2622190 T3	05-07-2017
			HU E033757 T2	28-12-2017
			JP 6292721 B2	14-03-2018
			JP 2015522067 A	03-08-2015
			KR 20150036035 A	07-04-2015
			LT 2872497 T	25-04-2017
			PL 2872497 T3	31-07-2017
			PT 2872497 T	24-04-2017
			SI 2872497 T1	31-08-2017
			WO 2014011047 A1	16-01-2014

WO 2017060432	A1	13-04-2017	EP 3359521 A1	15-08-2018
			HK 1257665 A1	25-10-2019
			JP 6639656 B2	05-02-2020
			JP 2018531250 A	25-10-2018
			JP 2020073524 A	14-05-2020
			US 2018305328 A1	25-10-2018
			US 2021024484 A1	28-01-2021
			WO 2017060432 A1	13-04-2017

WO 2019101826	A1	31-05-2019	AU 2018371153 A1	04-06-2020
			BR 112020010089 A2	03-11-2020
			CA 3079483 A1	31-05-2019
			CN 111417393 A	14-07-2020
			EP 3713564 A1	30-09-2020
			JP 2021504307 A	15-02-2021
			KR 20200090818 A	29-07-2020
			SG 11202003743S A	29-06-2020
			US 2020345706 A1	05-11-2020

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2020/050782

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2019101826 A1	31-05-2019

WO 2009061744	A2	14-05-2009	
		CA 2704473 A1	14-05-2009
		DK 2220030 T3	11-04-2016
		DK 3456707 T3	20-07-2020
		EA 201000756 A1	30-12-2010
		EA 201791981 A1	31-01-2018
		EP 2220030 A2	25-08-2010
		EP 3018122 A1	11-05-2016
		EP 3456707 A1	20-03-2019
		EP 3733642 A1	04-11-2020
		ES 2564179 T3	18-03-2016
		HK 1143804 A1	14-01-2011
		HU E028502 T2	28-12-2016
		JP 5755881 B2	29-07-2015
		JP 2011503005 A	27-01-2011
		JP 2014098025 A	29-05-2014
		JP 2016065103 A	28-04-2016
		JP 2018021080 A	08-02-2018
		JP 2019131618 A	08-08-2019
		JP 2020200344 A	17-12-2020
		MX 338572 B	22-04-2016
		PL 2220030 T3	29-07-2016
		PL 3456707 T3	21-09-2020
		SI 2220030 T1	29-04-2016
		SI 3456707 T1	30-10-2020
		US 2009118257 A1	07-05-2009
		US 2012122934 A1	17-05-2012
		US 2013289034 A1	31-10-2013
		US 2016075638 A1	17-03-2016
		US 2017313649 A1	02-11-2017
		US 2019270699 A1	05-09-2019
		WO 2009061744 A2	14-05-2009

WO 0243666	A2	06-06-2002	
		AU 3261602 A	11-06-2002
		CA 2427470 A1	06-06-2002
		CN 1477958 A	25-02-2004
		EP 1339404 A2	03-09-2003
		JP 2004514686 A	20-05-2004
		WO 0243666 A2	06-06-2002
