the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

The present inventors have surprisingly found that these objects can be achieved by the compounds of the general formula (I) as described hereinafter.

Summary of the invention

Accordingly, the present ~~invention~~disclosure relates to a compound of general formula (I).

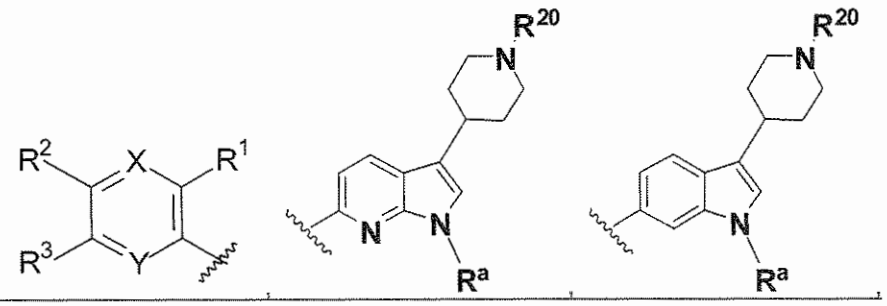
In one aspect, the present invention relates to a compound of formula (I):

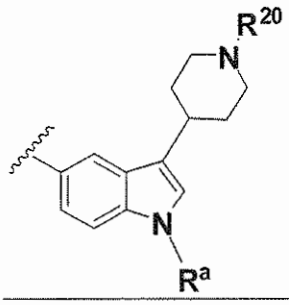
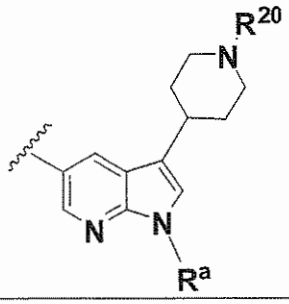
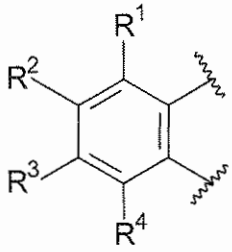
$$A\text{–}L_1\text{–}B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

wherein

A is selected from the group consisting of:

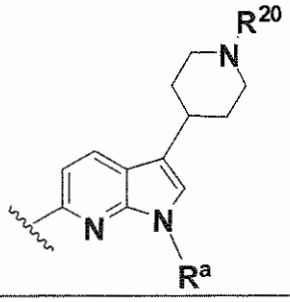
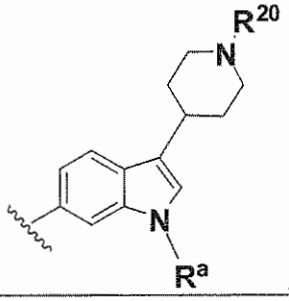
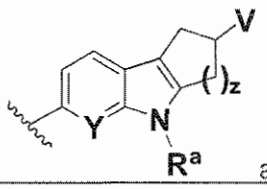


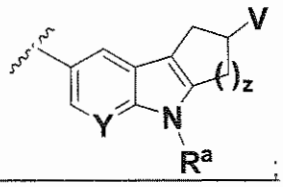



and

L_1 is


;

B is selected from the group consisting of:

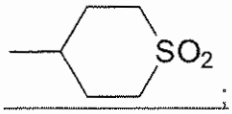



and


;

wherein

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $-CONR^{30}R^{31}$, $-N(R^{30})-C(O)-R^{31}$, alkyl, -O-alkyl, -C(O)O-alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl,

cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if any of the groups $R^1/R^2/R^3/R^4$ are adjacent, they can optionally be taken together and can form a 5- to 8-membered ring containing carbon atoms and optionally one or more heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 5- to 8-membered ring may be substituted by $NR^{20}R^{21}$ or –O–alkyl, wherein the alkyl can be optionally substituted, or by



;

for each occurrence, R^a is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, $S(O)_tNR^{30}R^{31}$, $S(O)_tR^{30}$, $C(O)OR^{30}$, $C(O)R^{30}$, and $C(O)NR^{30}R^{31}$;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted, or wherein R^{20} and R^{21}, when taken together with the nitrogen to which they are attached, can form a 3- to 8-membered ring containing carbon atoms and optionally one or more further heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 3- to 8-membered ring may be optionally substituted;

X and Y are each independently selected from the group consisting of CR^b and N;

t is 1 or 2; and

V is absent or $NR^{20}R^{21}$

z is 1 or 2.

In a further aspect, the present invention relates to a radiopharmaceutical formulation comprising a compound according to the present invention comprising a radionuclide.

In a further aspect, the present invention relates to a pharmaceutical composition comprising a compound according to the present invention wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient. Also disclosed is a pharmaceutical composition or a radiopharmaceutical formulation comprising a compound of general formula (I).

In a further aspect, the present invention relates to the use of the compound according to the present invention, for the preparation of a medicament for treating or preventing a disease or condition associated with an amyloid and/or amyloid-like protein, wherein the disease is a neurological disorder selected from the group consisting of Alzheimer's disease (AD), Lewy body dementia (LBD), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), the Guam Parkinson-Dementia complex or mild cognitive impairment (MCI) or wherein the disease is progressive supranuclear palsy, multiple sclerosis, inclusion-body myositis (IBM), Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, amyotropic lateral sclerosis (ALS), inclusion-body myositis (IBM), adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

Also disclosed herein is ~~Yet another aspect of the present invention relates to~~ the use of a compound of general formula (I) for the preparation of a medicament for the treatment of diseases or conditions associated with amyloid or amyloid-like proteins, including amyloidosis.

In a further aspect, the present invention relates to the use of the compound according to the present invention for the preparation of a medicament for treating or preventing an ocular disease or condition associated with a pathological abnormality/change in the tissue of the visual system, particularly associated with an amyloid-beta-related pathological abnormality/change in the tissue of the visual system, wherein the ocular disease or condition is selected from the group consisting of neuronal degradation, cortical visual deficits, glaucoma, cataract due to beta-amyloid deposition, ocular amyloidosis, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

Also disclosed herein is a method of treating diseases or conditions associated with amyloid or amyloid-like proteins, comprising administering to a subject in need of such treatment an effective amount of a compound of general formula (I).

Also disclosed herein is ~~Yet another aspect of the present invention relates to~~ the use of a compound of general formula (I) for the preparation of a medicament for treating or alleviating the effects of ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system.

Also disclosed herein is a method of treating or alleviating the effects of ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system comprising administering to a subject in need of such treatment an effective amount of a compound of general formula (I).

The ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system are particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as, for example, neuronal degradation. Said pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

In a further aspect the invention relates to a mixture comprising a compound according to the present invention and optionally at least one further biologically active compound and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient, wherein the further biologically active compound is selected from the group consisting of antibodies, vaccines, compounds against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepin and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), α-secretase activators, β- and γ-secretase inhibitors, tau proteins, neurotransmitters, β-sheet breakers, attractants for amyloid beta clearing / depleting cellular components, inhibitors of N-terminal truncated amyloid beta including pyroglutamated amyloid beta 3-42, anti-inflammatory molecules, or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine, M1 agonists and other drugs including any amyloid or tau modifying drug and nutritive supplements. Also disclosed herein is a mixture (such as a pharmaceutical composition) comprising a compound according to the present invention and optionally at least one further biologically active compound and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient. The further biologically active substance can be a known compound used in the medication of diseases and disorders which are caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of diseases and disorders associated with amyloid or amyloid-like protein such as the Aβ protein involved in Alzheimer's disease.

The further biologically active substance or compound may exert its biological effect by the same or a similar mechanism as the compound according to the invention or by an unrelated mechanism of action or by a multiplicity of related and/or unrelated mechanisms of action.

In a further aspect, the present invention relates to an *in vitro*~~A~~ method of collecting data for the diagnosis of an amyloid-associated disease or condition in a sample or a patient is also disclosed which comprises:

(a) bringing a sample or a specific body part or body area suspected to contain an amyloid protein into contact with a compound according to the present invention;

(b) allowing the compound to bind to the amyloid protein;

(c) detecting the compound bound to the protein; and

(d) optionally correlating the presence or absence of compound binding with the amyloid protein with the presence or absence of amyloid protein in the sample or specific body part or area.

In yet a further aspect the invention relates to an *in vitro*~~Another embodiment of the present invention is a~~ method of determining the extent of amyloidogenic plaque burden in a tissue and/or a body fluid comprising:

(a) providing a sample representative of the tissue and/or body fluid under investigation;

(b) testing the sample for the presence of amyloid protein with a compound according to the present invention;

(c) determining the amount of compound bound to the amyloid protein; and

(d) calculating the plaque burden in the tissue and/or body fluid.

A further aspect relates to an *in vitro* method of collecting data for determining a predisposition to an amyloid-associated disease or condition in a patient comprising detecting the specific binding of a compound according to the present invention to an amyloid protein in a sample or *in situ* which comprises the steps of:

(a) bringing the sample or a specific body part or body area suspected to contain the amyloid protein into contact with a compound according to the present invention, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample or specific body part or area; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

Yet another aspect of the present invention is *an in vitro* method of collecting data for monitoring minimal residual disease in a patient following treatment with an antibody or a vaccine composition, wherein the method comprises:

(a) bringing a sample or a specific body part or body area suspected to contain an amyloid protein into contact with a compound according to the present invention, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample or specific body part or body area; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

Yet another aspect of the present invention is an *in vitro*~~A~~ method of collecting data for predicting responsiveness of a patient being treated with an antibody or a vaccine composition is also described which comprises:

(a) bringing a sample or a specific body part or body area suspected to contain an amyloid protein into contact with a compound according to the present invention, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample or specific body part or body area; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

Also disclosed~~A further aspect of the present invention~~ is a test kit for detection and diagnosis of an amyloid-associated disease or condition comprising a compound according to the present invention.

In another aspect of the present invention a compound according to the present invention is for use in inhibiting protein aggregation, in particular for use in inhibiting Aβ1-42 aggregation, Tau aggregation or alpha-synuclein aggregation

In one aspect of the invention the use of the compound according to the present invention is disclosed for the preparation of a medicament for (a) reducing the β-amyloid plaque load, and/or (b) inhibiting the formation of β-amyloid plaques and/or (c) retarding the increase of amyloid load in the brain of a patient.

A further ~~embodiment~~example of the ~~invention~~present disclosure provides a method of (a) reducing the β-amyloid plaque load, and/or (b) inhibiting the formation of β-amyloid plaques and/or (c) retarding the increase of

amyloid load in the brain of a subject comprising administering to a subject in need of such treatment an effective amount of a compound according to the present invention.

In yet another ~~embodiment~~example a compound according to the present ~~invention~~disclosure is for use in (a) the reduction of the β-amyloid plaque load, and/or (b) the inhibition of the formation of β-amyloid plaques and/or (c) the retardation of the increase of amyloid load in the brain of a patient.

Also disclosed is~~According to a further aspect the present invention relates to~~ the use of the compound according to the present invention for the preparation of a medicament for retaining or increasing cognitive memory capacity in a subject suffering from memory impairment.

Also disclosed is~~According to another aspect the present invention provides~~ a method of retaining or increasing cognitive memory capacity in a subject suffering from memory impairment comprising administering to a subject in need of such treatment an effective amount of a compound according to the present invention.

Yet another aspect of the present invention relates to a compound according to the present invention for use in the retention or increase of cognitive memory capacity in a subject suffering from memory impairment.

Preferred embodiments of the invention are summarized in the dependent claims.

The individual compounds which are known from WO 2007/002433 are not included in the scope of the claims relating to the compounds or the pharmaceutical composition. The compounds are, for example, listed in the following:

