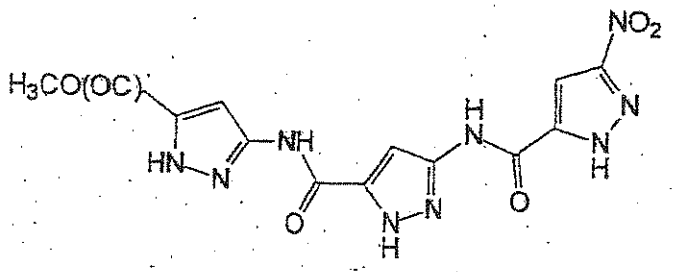
N- (METHYL) -1H- PYRAZOL- 3 -AMINE, N- (METHYL) -PYRIDIN-2-AMINE AND N- (METHYL) –THIAZOL-2-AMINE DERIVATIVES FOR THE TREATMENT OF DISEASES ASSOCIATED WITH AMYLOID OR AMYLOID-LIKE PROTEINS, LIKE E.G. ALZHEIMER'S

The present invention relates to novel compounds that can be employed in the treatment of a group of disorders and abnormalities associated with amyloid protein, such as Alzheimer's disease, and of diseases or conditions associated with amyloid-like proteins. The present invention further relates to pharmaceutical compositions comprising these compounds and to the use of these compounds for the preparation of medicaments for the treatment of diseases or conditions associated with amyloid or amyloid-like proteins. A method of treating diseases or conditions associated with amyloid or amyloid-like proteins is also disclosed.

The compounds of the present invention can also be used in the treatment of ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as 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 amyloidoses; 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.



"Trimer"

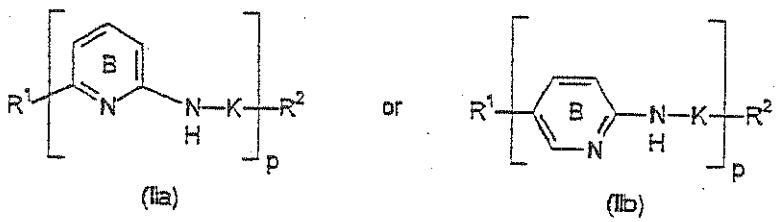
Some of the molecules described in WO 03/095429 are said to have an inhibiting effect on the formation of aggregates of Aβ in two biophysical assays. According to Rzepecki et al., Synthesis (2003) 12, 1815-1826 one of the molecules described therein was able to reduce the aggregation of a recombinant PrP^C in solution. Physicochemical properties, however, were not investigated in these studies.

Physicochemical properties play a key role in the penetration of the blood-brain barrier by neurotherapeutics. Factors relevant to the success of CNS drugs have been reviewed (H. Pajouhesh and G.R. Lenz, NeuroRx®: J. Am. Soc. Exp. Neurother. (2005) Vol. 2, 541). These include the partition coefficient between water and n-octanol (LogP), i.e. basically the lipophilicity of the compound. Some of the compounds described in WO 03/095429 and Rzepecki et al., Synthesis (2003) 12, 1815-1826 have an unfavorable calculated LogP and are, therefore, not expected to pass the blood-brain barrier. In particular, "AmpOx" has a calculated LogP below zero.

Other compounds described in the above documents have properties that make them unsuitable for administration to a patient due to their deleterious side-effects. For example, "Trimer" is mutagenic, carcinogenic and metabolically unstable.

Summary

In one aspect, there is provided a compound having the general formula (IIa) or (IIb)



(IIa) (IIb)

wherein

p is 2 or 3;

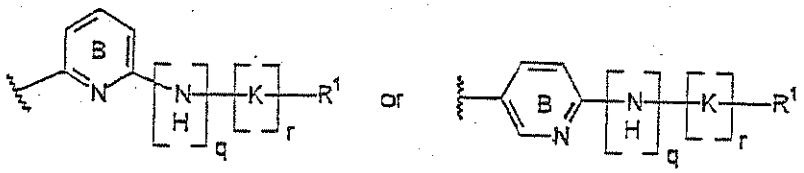
each linker K is independently C_{1-3} alkylene which is optionally substituted by one or more C_{1-4} alkyl groups;

the heterocyclic ring B is optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, mono- and di-C_{1-4} alkyl amino, C_{3-7} cycloalkyl amino, and 5- or 6- membered saturated heterocyclyl, or two substituents may be joined to form a saturated, unsaturated or aromatic 5- to 7-membered ring which is fused with the heterocyclic ring B;

R^1 is selected from –H, –halogen, $-C_{1-4}$ alkyl, $-NH_2$, $-NH-C_{1-4}$ alkyl, $-C_{1-4}$ alkylene–NH_2, $-C_{1-4}$ alkylene–$NH-C_{1-4}$ alkyl, –aryl, –aryl–R^3, $-C_{1-4}$ alkylene–aryl, $-C_{1-4}$ alkylene–aryl–R^3, –heteroaryl, –heteroaryl–R^3, $-NH-C_{1-4}$ alkylene–aryl, $-NH-C_{1-4}$ alkylene–aryl–R^3, –OH and $-O-C_{1-4}$ alkyl; and

R^3 is C_{1-4} alkyl, halogen, OH or $O-C_{1-4}$ alkyl;

R^2 is –H, $-C_{1-4}$ alkyl, –aryl or a group of the formula (IIIa) or (IIIb)



(IIIa) (IIIb)

wherein B, K and R^1 are as defined above, q is 0 or 1 and r is 0 or 1.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above.

In yet another aspect, there is provided the use of a compound as defined above 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, preferably selected from

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 amyloidoses, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

In yet another aspect, there is provided the compound as defined above for use in treatment or prevention of a disease or condition associated with an amyloid and/or amyloid-like protein, wherein the disease is a neurological disorder, preferably selected from 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 amyloidoses, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

In yet another aspect, there is provided a mixture comprising a compound as defined above and optionally at least one further biologically active compound and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

In yet another aspect, there is provided an *in vitro* method of collecting data for the diagnosis of an amyloid-associated disease or condition in a sample comprising:

(a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined above;

(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.

In yet another aspect, there is provided a *in vitro* method of determining the extent of amyloidogenic plaque burden in a sample comprising:

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

(b) testing the sample for the presence of amyloid protein with a compound as defined above;

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

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

In yet another aspect, there is provided 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 as defined above to an amyloid protein in a sample which comprises the steps of:

(a) bringing the sample suspected to contain the amyloid protein into contact with a compound as defined above, 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; and

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

In yet another aspect, there is provided 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 suspected to contain an amyloid protein into contact with a compound as defined above, 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; and

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

In yet another aspect, there is provided an *in vitro* method of collecting data for predicating responsiveness of a patient being treated with an antibody or a vaccine composition comprising:

(a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined above, 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; and

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

In yet another aspect, there is provided a test kit for detection and/or diagnosis of an amyloid-associated disease or condition comprising a compound as defined above, wherein the disease is a neurological disorder, preferably selected from 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 amyloidoses, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

In yet another aspect, there is provided the use of the compound as defined above 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 amyloidoses, primary retinal degeneration, macular degeneration, for example

age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

In yet another aspect, there is provided a compound as defined above 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 amyloidoses, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

Detailed description

It was an object of the present invention to provide compounds that can be employed in the treatment of diseases or conditions associated with amyloid or amyloid-like proteins, including amyloidosis. The compounds should be able to pass the blood-brain barrier. Furthermore, they should be pharmaceutically acceptable, in particular, they should not have mutagenic or carcinogenic properties or be metabolically unstable.

Sequence Listing

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<150> EP 06024427.4
<151> 2006-11-24

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50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu Val
        35                  40                  45

Ala Ser Ile Asn Ser Asn Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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     50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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                85                  90                  95

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
        115                 120                 125

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
            180                 185                 190

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
    210                 215                 220

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225                 230                 235                 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                245                 250                 255

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
            260                 265                 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
        275                 280                 285

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Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
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        355                 360                 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    370                 375                 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385                 390                 395                 400

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
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Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            420                 425                 430

Leu Ser Leu Ser Leu Gly Lys
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