molecules to be effective in treating cognitive decline and motor activity, they must cross the blood-brain barrier (BBB). Transport across the BBB is the exception not the rule, and 98% of all small molecules do not cross it. (Pardridge, William M, *The Blood-Brain Barrier: Bottleneck in Brain Drug Development*, NeuroRx: The J. of the Am. Society for Experimental NeuroTherapeutics, 2:3-14, 2005). As a result, therapies for neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), are limited; in fact, Alzheimer's has one of the highest failure rates for clinical development of any disease area (99.6% failure in the last 20 years). (*Id.;* and Burke, M., *Renewed focus on dementia checked by drug challenges*, ChemistryWorld, Jul. 3, 2014). Those BBB-permeable drugs that are approved for treatment of cognitive disease like Alzheimer's, such as donepezil, exhibit temporary effects and do not work on all patients. (Banks, W.A., *Drug Delivery to the Brain in Alzheimer's Disease: Consideration of the Blood-brain Barrier*, Adv. Drug. Deliv. Rev. 64(7):629-39 (2012); and Burke, M. *supra*). Similarly, levodopa which treats Parkinson's disease symptoms like motor deficits and crosses the BBB, eventually loses its efficacy. An additional hurdle for treatments that do cross the BBB is that making compounds more lipophilic (which tends to make them more BBB-penetrating) also often results in increased removal from the blood, leading to decreased bioavailability. Hence, the increase in lipophilicity offsets the plasma area under the curve (AUC), minimizing brain uptake. (Pardridge, William M, *supra*).

III. Summary

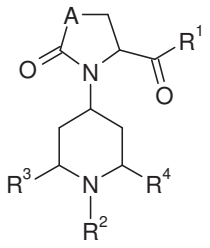
The present disclosure overcomes these drawbacks. For example, Compound 1, a compound of the disclosure, has exhibited resistance in crossing the BBB in significant concentrations yet unexpectedly results in improvement of symptoms associated with age-related neurodegeneration and age-related motor decline. Thus, the present disclosure can act in a peripheral manner, forgoing what was considered to be a requirement for effective cognitive-acting pharmaceuticals, *i.e.* to work directly on central nervous system. And although certain examples of the disclosure may cross the BBB in significant concentrations, their ability to

antagonize the CCL11/CCR3 pathway offers an alternative mechanism of action to current therapy for cognitive and motor defects.

The compounds of the disclosure act as antagonists of c-c motif chemokine receptor 3 (CCR3), the receptor for Eotaxin-1. Eotaxin-1 (CCL11) is a protein that is increased in levels in blood plasma with aging and which has been shown to cause decreases in cognitive function. (Villeda *et al., The aging systemic milieu negatively regulates neurogenesis and cognitive function*, Nature, 477(7362):90-94 (2011)). Eotaxin/CC11 acts primarily on the G-protein coupled receptor CCR3 which is expressed on eosinophils in the periphery and on neurons and glial cells in the central nervous system. (Xia, M, *et al.*, *Immunohistochemical Study of the β-Chemokine Receptors CCR3 and CCR5 and Their Ligands in the Normal and Alzheimer's Disease Brains*, Am. J. Pathol. 153(1);31-37 (1998)). In Alzheimer's disease, it has been observed that CCR3 levels are increased in the CNS. (*Id.*) The cognitive effects of antagonizing CCR3 in Alzheimer's disease and related disorders would thus be expected to be mediated by centrally located eotaxin-1/CCR3 interaction. However, Compound 1 (a compound of the disclosure), unexpectedly resulted in improving cognitive function and stimulating neurogenesis despite its inability to cross the BBB in significant concentrations.

Methods of treating patients for aging-associated impairments, neurodegenerative disease and associated cognitive and motor decline are provided, including by way of example and not limitation, Alzheimer's disease, Parkinson's disease, Dementia with Lewy Bodies, frontotemporal dementia, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, glaucoma, myotonic dystrophy, vascular dementia, progressive supranuclear palsy, and the like. Examples of the methods include modulation of CCR3, the principal receptor of CCL11/eotaxin-1 through the administration of a therapeutically effective amount of CCR3 antagonists of the disclosure. The methods include administering an effective therapeutic dose of CCR3 antagonists to subjects or patients as well as monitoring for specific clinical endpoints. Also included are methods of treating neurodegenerative disease and associated cognitive and motor decline with an agent that acts peripherally, i.e. does not cross the blood-brain barrier in significant concentrations, yet exhibits improvement in the disease, such as improved cognition or motor activity.

In one aspect, the present disclosure provides use of a compound of formula 1 in the manufacture of a medicament for treating neurodegenerative disease in a subject diagnosed with the neurodegenerative disease,



1

wherein

A is CH_2, O or N-C_{1-6}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;
- a $C_{9\ or\ 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, methoxy-phenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with halogen or CN;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazole;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-haloalkyl, C_{1-6}-alkylene-OH, C_{2-6}-alkenylene-OH, C_{2-6}-alkynylene-OH, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH\text{-}C_{3-6}$-cycloalkyl, CN, CO-pyridinyl, $CONR^{1.1.1}R^{1.1.2}$, $COO\text{-}C_{1-6}$-alkyl, $N(SO_2\text{-}C_{1-6}\text{-alkyl})(CH_2CON(C_{1-4}\text{-alkyl})_2)$ $O\text{-}C_{1-6}$-alkyl, O-pyridinyl, $SO_2\text{-}C_{1-6}$-alkyl, $SO_2\text{-}C_{1-6}$-alkylen-OH, $SO_2\text{-}C_{3-6}$-cycloalkyl, SO_2-piperidinyl, $SO_2NH\text{-}C_{1-6}$-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl and =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ H, C_{1-6}-alkyl, SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one N or O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-4}-alkylene-OH, OH, =O;

or

$R^{1.1}$ is phenyl, wherein two adjacent residues are together forming a five- or six-membered carbocyclic aromatic or non-aromatic ring, optionally containing independently from each other one or two N, S, or SO_2, replacing a carbon atom of the ring, wherein the ring is optionally substituted with C_{1-4}-alkyl or =O;

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl,

CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, $COR^{1.2.3}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, $SO_2N(C_{1-6}$-alkyl$)_2$ or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;

- heteroaryl, optionally substituted with a five- or six-membered carbocyclic non-aromatic ring containing independently from each other two N, O, S, or SO_2, replacing a carbon atom of the ring;
- a aromatic or non-aromatic $C_{9\ or\ 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by N, O or S each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}$-alkyl$)_2$, CONH-C_{1-6}-alkyl, =O;
- a heterocyclic non-aromatic ring, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-6}-alkyl,

$R^{1.2.1}$ H, C_{1-6}-alkyl, C_{1-6}-alkylene-C_{3-6}-cycloalkyl, C_{1-4}-alkylene-phenyl, C_{1-4}-alkylene-furanyl, C_{3-6}-cycloalkyl, C_{1-4}-alkylene-O-C_{1-4}-alkyl, C_{1-6}-haloalkyl or a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring, optionally substituted with 4-cyclopropylmethyl-piperazinyl

$R^{1.2.2}$ H, C_{1-6}-alkyl;

$R^{1.2.3}$ a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring;

$R^{1.3}$ is selected from phenyl, heteroaryl or indolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, phenyl, heteroaryl;

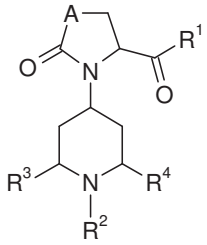
R^2 is selected from the group consisting of C_{1-6}-alkylene-phenyl, C_{1-6}-alkylene-naphthyl, and C_{1-6}-alkylene-heteroaryl; each optionally substituted with one, two or three residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen;

R^3 is H, C_{1-6}-alkyl;

R^4 is H, C_{1-6}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

In one aspect, the present disclosure provides a compound of formula 1 for use in treating neurodegenerative disease in a subject diagnosed with the neurodegenerative disease,



1

wherein

A is CH_2, O or N-C_{1-6}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;
- a $C_{9\ or\ 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two

residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, methoxy-phenyl;

- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with halogen or CN;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazole;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-haloalkyl, C_{1-6}-alkylene-OH, C_{2-6}-alkenylene-OH, C_{2-6}-alkynylene-OH, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, CO-pyridinyl, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-6}-alkyl, $N(SO_2\text{-}C_{1-6}\text{-alkyl})(CH_2CON(C_{1-4}\text{-alkyl})_2)$ O-C_{1-6}-alkyl, O-pyridinyl, SO_2-C_{1-6}-alkyl, SO_2-C_{1-6}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-6}-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl and =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ H, C_{1-6}-alkyl, SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one N or O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-4}-alkylene-OH, OH, =O;

or

$R^{1.1}$ is phenyl, wherein two adjacent residues are together forming a five- or six-membered carbocyclic aromatic or non-aromatic ring, optionally containing independently from each other one or two N, S, or SO_2, replacing a carbon atom of the ring, wherein the ring is optionally substituted with C_{1-4}-alkyl or =O;

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, $COR^{1.2.3}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, $SO_2N(C_{1-6}$-alkyl$)_2$ or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;
- heteroaryl, optionally substituted with a five- or six-membered carbocyclic non-aromatic ring containing independently from each other two N, O, S, or SO_2, replacing a carbon atom of the ring;
- a aromatic or non-aromatic $C_{9\text{ or }10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by N, O or S each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}$-alkyl$)_2$, CONH-C_{1-6}-alkyl, =O;
- a heterocyclic non-aromatic ring, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-6}-alkyl,

$R^{1.2.1}$ H, C_{1-6}-alkyl, C_{1-6}-alkylene-C_{3-6}-cycloalkyl, C_{1-4}-alkylene-phenyl, C_{1-4}-alkylene-furanyl, C_{3-6}-cycloalkyl, C_{1-4}-alkylene-O-C_{1-4}-alkyl, C_{1-6}-haloalkyl or a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring, optionally substituted with 4-cyclopropylmethyl-piperazinyl

$R^{1.2.2}$ H, C_{1-6}-alkyl;

$R^{1.2.3}$ a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring;

$R^{1.3}$ is selected from phenyl, heteroaryl or indolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, phenyl, heteroaryl;

R^2 is selected from the group consisting of C_{1-6}-alkylene-phenyl, C_{1-6}-alkylene-naphthyl, and C_{1-6}-alkylene-heteroaryl; each optionally substituted with one, two or three residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen;

R^3 is H, C_{1-6}-alkyl;

R^4 is H, C_{1-6}-alkyl;

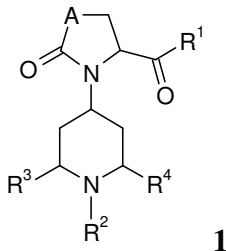
or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

IV. Incorporation by Reference

Claims

What is claimed:

1. Use of a compound of formula 1 in the manufacture of a medicament for treating neurodegenerative disease in a subject diagnosed with the neurodegenerative disease,



1

wherein

A is CH_2, O or N-$C_{1\text{-}6}$-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-$C_{3\text{-}6}$-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl, O-$C_{1\text{-}6}$-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-$C_{1\text{-}6}$-alkyl, COO-$C_{1\text{-}6}$-alkyl;
- a $C_{9\text{ or }10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of $C_{1\text{-}6}$-alkyl, COO-$C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-haloalkyl, O-$C_{1\text{-}6}$-alkyl, NO_2, halogen, CN, $NHSO_2$-$C_{1\text{-}6}$-alkyl, methoxy-phenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-$C_{1\text{-}6}$-alkyl, NHCH(CH_2O-$C_{1\text{-}6}$-alkyl)-benzoimidazolyl, optionally substituted with halogen or CN;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazole;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-haloalkyl, C_{1-6}-alkylene-OH, C_{2-6}-alkenylene-OH, C_{2-6}-alkynylene-OH, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH\text{-}C_{3-6}$-cycloalkyl, CN, CO-pyridinyl, $CONR^{1.1.1}R^{1.1.2}$, $COO\text{-}C_{1-6}$-alkyl, $N(SO_2\text{-}C_{1-6}\text{-alkyl})(CH_2CON(C_{1-4}\text{-alkyl})_2)$ $O\text{-}C_{1-6}$-alkyl, O-pyridinyl, $SO_2\text{-}C_{1-6}$-alkyl, $SO_2\text{-}C_{1-6}$-alkylen-OH, $SO_2\text{-}C_{3-6}$-cycloalkyl, SO_2-piperidinyl, $SO_2NH\text{-}C_{1-6}$-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl and =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ H, C_{1-6}-alkyl, SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one N or O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-4}-alkylene-OH, OH, =O;

or

$R^{1.1}$ is phenyl, wherein two adjacent residues are together forming a five- or six-membered carbocyclic aromatic or non-aromatic ring, optionally containing independently from each other one or two N, S, or SO_2, replacing a carbon atom of the ring, wherein the ring is optionally substituted with C_{1-4}-alkyl or =O;

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, $COR^{1.2.3}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, $SO_2N(C_{1-6}\text{-alkyl})_2$ or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;
- heteroaryl, optionally substituted with a five- or six-membered carbocyclic non-aromatic ring containing independently from each other two N, O, S, or SO_2, replacing a carbon atom of the ring;
- a aromatic or non-aromatic $C_{9\text{ or }10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by N, O or S each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}\text{-alkyl})_2$, CONH-$C_{1-6}$-alkyl, =O;
- a heterocyclic non-aromatic ring, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-6}-alkyl,

$R^{1.2.1}$ H, C_{1-6}-alkyl, C_{1-6}-alkylene-C_{3-6}-cycloalkyl, C_{1-4}-alkylene-phenyl, C_{1-4}-alkylene-furanyl, C_{3-6}-cycloalkyl, C_{1-4}-alkylene-O-C_{1-4}-alkyl, C_{1-6}-haloalkyl or a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring, optionally substituted with 4-cyclopropylmethyl-piperazinyl

$R^{1.2.2}$ H, C_{1-6}-alkyl;

$R^{1.2.3}$ a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring;

$R^{1.3}$ is selected from phenyl, heteroaryl or indolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, phenyl, heteroaryl;

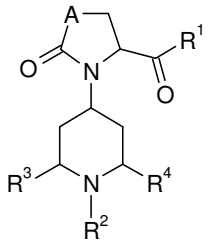
R^2 is selected from the group consisting of C_{1-6}-alkylene-phenyl, C_{1-6}-alkylene-naphthyl, and C_{1-6}-alkylene-heteroaryl; each optionally substituted with one, two or three residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen;

R^3 is H, C_{1-6}-alkyl;

R^4 is H, C_{1-6}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

2. A compound of formula 1 for use in treating neurodegenerative disease in a subject diagnosed with the neurodegenerative disease,



1

wherein

A is CH_2, O or N-C_{1-6}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected

from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;

- a $C_{9\ or\ 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, methoxy-phenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with halogen or CN;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazole;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-haloalkyl, C_{1-6}-alkylene-OH, C_{2-6}-alkenylene-OH, C_{2-6}-alkynylene-OH, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, CO-pyridinyl, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-6}-alkyl, $N(SO_2\text{-}C_{1-6}\text{-alkyl})(CH_2CON(C_{1-4}\text{-alkyl})_2)$ O-C_{1-6}-alkyl, O-pyridinyl, SO_2-C_{1-6}-alkyl, SO_2-C_{1-6}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-6}-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl and =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ H, C_{1-6}-alkyl, SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one N or O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-4}-alkylene-OH, OH, =O;

or

$R^{1.1}$ is phenyl, wherein two adjacent residues are together forming a five- or six-membered carbocyclic aromatic or non-aromatic ring, optionally containing independently from each other one or two N, S, or SO_2, replacing a carbon atom of the ring, wherein the ring is optionally substituted with C_{1-4}-alkyl or =O;

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, $COR^{1.2.3}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, $SO_2N(C_{1-6}$-alkyl$)_2$ or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;
- heteroaryl, optionally substituted with a five- or six-membered carbocyclic non-aromatic ring containing independently from each other two N, O, S, or SO_2, replacing a carbon atom of the ring;
- a aromatic or non-aromatic $C_{9\text{ or }10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by N, O or S each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}$-alkyl$)_2$, CONH-C_{1-6}-alkyl, =O;
- a heterocyclic non-aromatic ring, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-6}-alkyl,

$R^{1.2.1}$ H, C_{1-6}-alkyl, C_{1-6}-alkylene-C_{3-6}-cycloalkyl, C_{1-4}-alkylene-phenyl, C_{1-4}-alkylene-furanyl, C_{3-6}-cycloalkyl, C_{1-4}-alkylene-O-C_{1-4}-alkyl,

C_{1-6}-haloalkyl or a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring, optionally substituted with 4-cyclopropylmethyl-piperazinyl

$R^{1.2.2}$ H, C_{1-6}-alkyl;

$R^{1.2.3}$ a five- or six-membered carbocyclic non-aromatic ring, optionally containing independently from each other one or two N, O, S, or SO_2, replacing a carbon atom of the ring;

$R^{1.3}$ is selected from phenyl, heteroaryl or indolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, phenyl, heteroaryl;

R^2 is selected from the group consisting of C_{1-6}-alkylene-phenyl, C_{1-6}-alkylene-naphthyl, and C_{1-6}-alkylene-heteroaryl; each optionally substituted with one, two or three residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl, halogen;

R^3 is H, C_{1-6}-alkyl;

R^4 is H, C_{1-6}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

3. The use of claim 1 or the compound for use of claim 2 wherein the compound of formula 1,

A is CH_2, O or N-C_{1-4}-alkyl;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;

- $NHCH_2$-$R^{1.3}$;
- NH-C_{3-6}-cycloalkyl, whereas optionally one carbon atom is replaced by a nitrogen atom, whereas the ring is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, O-C_{1-6}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen, CN, SO_2-C_{1-6}-alkyl, COO-C_{1-6}-alkyl;
- a $C_{9\ or\ 10}$-bicyclic-ring, whereas one or two carbon atoms are replaced by nitrogen atoms and the ring system is bound via a nitrogen atom to the basic structure of formula **1** and whereas the ring system is optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, COO-C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, NO_2, halogen, CN, $NHSO_2$-C_{1-6}-alkyl, m-methoxyphenyl;
- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-6}-alkyl, NHCH(CH_2O-C_{1-6}-alkyl)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, SO_2-C_{1-6}-alkyl, SO_2-C_{1-6}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-6}-alkyl, $SO_2N(C_{1-6}\text{-alkyl})_2$, halogen, CN, CO-morpholinyl, CH_2-pyridinyl or a heterocyclic ring optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, NHC_{1-6}-alkyl,, =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl, $CH_2CON(C_{1-6}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-6}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-6}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-6}-alkyl;

$R^{1.1.2}$ H, C_{1-6}-alkyl, SO_2C_{1-6}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- heteroaryl, optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-6}-alkyl, $CONR^{1.2.1}R^{1.2.2}$, COO-C_{1-6}-alkyl, $CONH_2$, O-C_{1-6}-alkyl, halogen, CN, CO-pyrrolidinyl, CO-morpholinyl or heteroaryl optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-6}\text{-alkyl})_2$, $CONH$-C_{1-6}-alkyl, =O;
- piperidinyl, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with $NHCO$-C_{1-6}-alkyl,

$R^{1.2.1}$ H, C_{1-6}-alkyl;

$R^{1.2.2}$ H, C_{1-6}-alkyl;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, O-C_{1-6}-haloalkyl;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl,

O-C_{1-6}-haloalkyl, halogen; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of halogen;

R^3 is H, C_{1-4}-alkyl;

R^4 is H, C_{1-4}-alkyl;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

4. The use of claim 1 or the compound for use of claim 2 wherein the compound of formula 1 is

A is CH_2, O or NMe;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-cyclohexyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, $NHSO_2$-phenyl, NHCONH-phenyl, halogen;
- NH-pyrrolidinyl, optionally substituted with one or two residues selected from the group consisting of SO_2-C_{1-4}-alkyl, COO-C_{1-4}-alkyl;
- piperidinyl, optionally substituted with one or two residues selected from the group consisting of $NHSO_2$-C_{1-4}-alkyl, m-methoxyphenyl;
- dihydro-indolyl, dihydro-isoindolyl, tetrahydro-quinolinyl or tetrahydro-isoquinolinyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, COO-C_{1-4}-alkyl, C_{1-4}-haloalkyl, O-C_{1-4}-alkyl, NO_2, halogen;

- a group selected from NHCH(pyridinyl)CH_2COO-C_{1-4}-alkyl, NHCH(CH_2O-C_{1-4}-alkyl)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-haloalkyl, $CH_2CON(C_{1-4}\text{-alkyl})_2$, $CH_2NHCONH$-C_{3-6}-cycloalkyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COO-C_{1-4}-alkyl, O-C_{1-4}-alkyl, SO_2-C_{1-4}-alkyl, SO_2-C_{1-4}-alkylen-OH, SO_2-C_{3-6}-cycloalkyl, SO_2-piperidinyl, SO_2NH-C_{1-4}-alkyl, $SO_2N(C_{1-4}\text{-alkyl})_2$, halogen, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, NHC_{1-4}-alkyl,, =O;

$R^{1.1.1}$ H, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-haloalkyl, $CH_2CON(C_{1-4}\text{-alkyl},)_2$, CH_2CO-azetindinyl, C_{1-4}-alkylen-C_{3-6}-cycloalkyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, C_{1-4}-alkylen-OH or thiadiazolyl, optionally substituted with C_{1-4}-alkyl;

$R^{1.1.2}$ H, C_{1-4}-alkyl, SO_2C_{1-4}-alkyl;

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- pyridinyl, pyridazinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, CH_2COO-C_{1-4}-alkyl, $CONR^{1.2.1}R^{1.2.2}$,

COO-C_{1-4}-alkyl, $CONH_2$, O-C_{1-4}-alkyl, halogen, CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl;

- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of $N(C_{1-4}\text{-alkyl})_2$, CONH-$C_{1-4}$-alkyl, =O;
- piperidinyl, optionally substituted with pyridinyl;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCO-C_{1-4}-alkyl,

$R^{1.2.1}$ H, C_{1-4}-alkyl;

$R^{1.2.2}$ H, C_{1-4}-alkyl;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, O-C_{1-4}-alkyl, O-C_{1-4}-haloalkyl;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-haloalkyl, O-C_{1-4}-haloalkyl, halogen; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of halogen;

R^3 is H;

R^4 is H;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

5. The use of claim 1 or the compound for use of claim 2 wherein formula 1 is

A is CH_2, O or NMe;

R^1 is selected from

- $NHR^{1.1}$, $NMeR^{1.1}$;
- $NHR^{1.2}$, $NMeR^{1.2}$;
- $NHCH_2$-$R^{1.3}$;
- NH-piperidinyl, optionally substituted with pyridinyl;
- NH-cyclohexyl, optionally substituted with one or two residues selected from the group consisting of t-Bu, $NHSO_2$-phenyl, NHCONH-phenyl, F;
- NH-pyrrolidinyl, optionally substituted with one or two residues selected from the group consisting of SO_2Me, COO-t-Bu;
- piperidinyl, optionally substituted with one or two residues selected from the group consisting of $NHSO_2$-n-Bu, m-methoxyphenyl;
- dihydro-indolyl, dihydro-isoindolyl, tetrahydro-quinolinyl or tetrahydro-isoquinolinyl, optionally substituted with one or two residues selected from the group consisting of Me, COOMe, CF_3, OMe, NO_2, F, Br;
- a group selected from NHCH(pyridinyl)CH_2COOMe, NHCH(CH_2OMe)-benzoimidazolyl, optionally substituted with Cl;
- or 1-aminocyclopentyl, optionally substituted with methyl-oxadiazolyl;

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, t-Bu, CF_3, CH_2CONMe_2, $CH_2NHCONH$-cyclohexyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COOMe, COOEt, OMe, SO_2Me, $SO_2CH_2CH_2OH$, SO_2Et, SO_2-cyclopropyl, SO_2-piperidinyl, SO_2NHEt, SO_2NMeEt, F, Cl, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl,

tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of Me, NHMe, =O;

$R^{1.1.1}$ H, Me, Et, t-Bu, i-Pr, cyclopropyl, CH_2-i-Pr, CH_2-t-Bu, $CH(CH_3)CH_2CH_3$, CH_2CHF_2, CH_2CONMe_2, CH_2CO-azetindinyl, CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, CH_2CH_2OH or thiadiazolyl, optionally substituted with Me;

$R^{1.1.2}$ H, Me, Et, SO_2Me, SO_2Et

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- pyridinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, Bu, cyclopropyl, CH_2COOEt, $CONR^{1.2.1}R^{1.2.2}$, COOMe, COOEt, $CONH_2$, OMe, Cl, Br CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted Me;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of NMe_2, CONHMe, =O;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCOMe,

$R^{1.2.1}$ H, Me;

$R^{1.2.2}$ H, Me;

$R^{1.3}$ is selected from phenyl, pyrazolyl, isoxazolyl, pyrimidinyl, indolyl or oxadiazolyl, each optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, cyclopentyl, OMe, $OCHF_2$;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of CH_3, CF_3, OCF_3, F, Cl, Br, Et; or CH_2-thiophenyl, optionally substituted with one or two residues selected from the group consisting of Cl, Br;

R^3 is H;

R^4 is H;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

6. The use of claim 1 or the compound for use of claim 2 wherein formula 1 is

A is CH_2, O or NMe;

R^1 is selected from

- $NHR^{1.1}$
- $NHR^{1.2}$,

$R^{1.1}$ is phenyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Bu, CF_3, CH_2CONMe_2, $CH_2NHCONH$-cyclohexyl, CN, $CONR^{1.1.1}R^{1.1.2}$, COOMe, COOEt, OMe, SO_2Me, $SO_2CH_2CH_2OH$, SO_2Et, SO_2-cyclopropyl, SO_2-piperidinyl, SO_2NHEt, SO_2NMeEt, F, Cl, CO-morpholinyl, CH_2-pyridinyl, or imidazolidinyl, piperidinyl, oxazinanyl, pyrazolyl, triazolyl,

tetrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrimidinyl, each optionally substituted with one or two residues selected from the group consisting of Me, NHMe, =O;

$R^{1.1.1}$ H, Me, Et, t-Bu, i-Pr, cyclopropyl, CH_2-i-Pr, CH_2-t-Bu, $CH(CH_3)CH_2CH_3$, CH_2CHF_2, CH_2CONMe_2, CH_2CO-azetindinyl, CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-pyranyl, CH_2-tetrahydrofuranyl, CH_2-furanyl, CH_2CH_2OH or thiadiazolyl, optionally substituted with Me;

$R^{1.1.2}$ H, Me, Et, SO_2Me, SO_2Et

or $R^{1.1.1}$ and $R^{1.1.2}$ together are forming a four-, five- or six-membered carbocyclic ring, optionally containing one O, replacing a carbon atom of the ring, optionally substituted with one or two residues selected from the group consisting of CH_2OH

$R^{1.2}$ is selected from

- pyridinyl, pyrrolyl, pyrazolyl, isoxazolyl, thiazolyl, thiadiazolyl, optionally substituted with one or two residues selected from the group consisting of Me, Et, Pr, Bu, cyclopropyl, CH_2COOEt, $CONR^{1.2.1}R^{1.2.2}$, COOMe, COOEt, $CONH_2$, OMe, Cl, Br CO-pyrrolidinyl, CO-morpholinyl or pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, each optionally substituted Me;
- benzothiazolyl, indazolyl, dihydro-indolyl, indanyl, tetrahydro-quinolinyl, each optionally substituted with one or two residues selected from the group consisting of NMe_2, CONHMe, =O;
- 4,5-dihydro-naphtho[2,1-d]thiazole, optionally substituted with NHCOMe,

$R^{1.2.1}$ H, Me;

$R^{1.2.2}$ H, Me;

R^2 is selected from CH_2-phenyl or CH_2-naphthyl, both optionally substituted with one or two residues selected from the group consisting of CH_3, CF_3, OCF_3, F, Cl, Br, Et

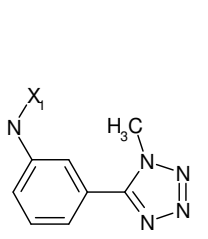
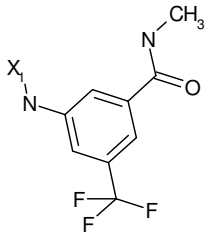
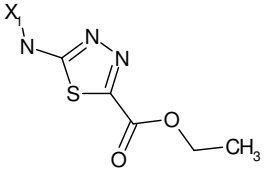
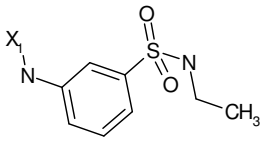
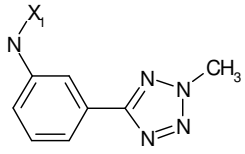
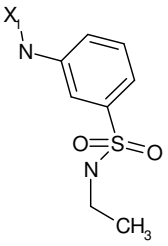
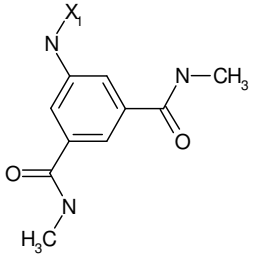
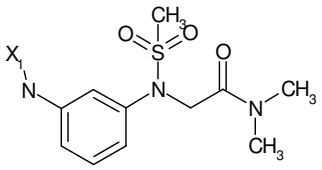
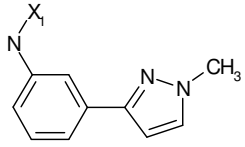
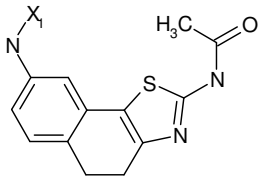
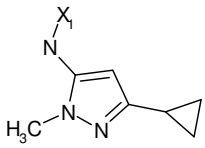
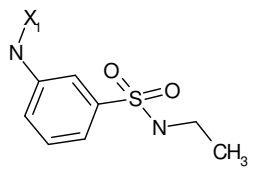
R^3 is H;

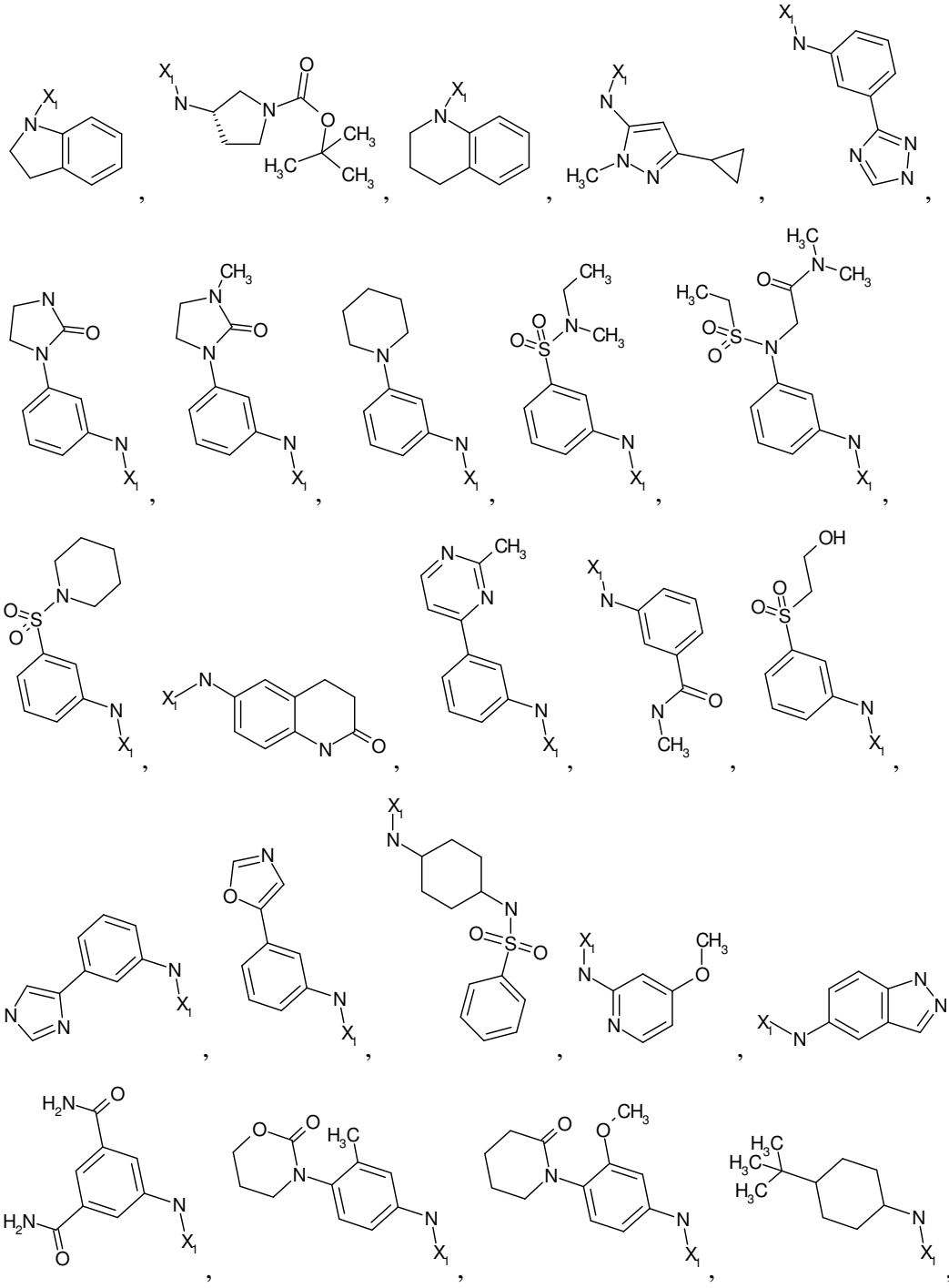
R^4 is H.

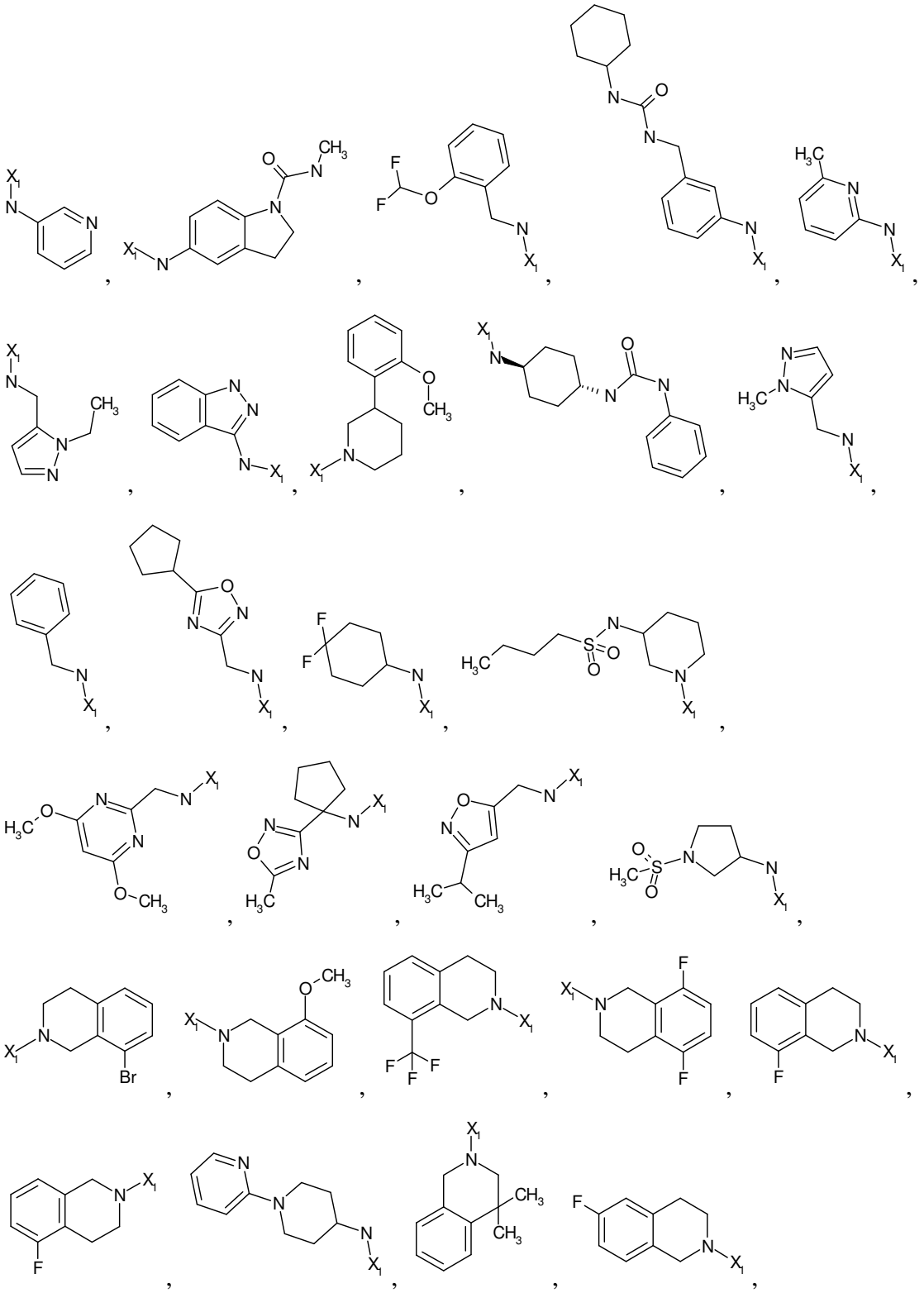
7. The use of claim 1 or the compound for use of claim 2 wherein formula 1 is

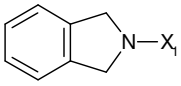
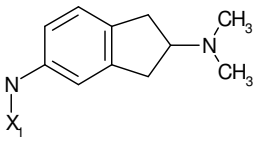
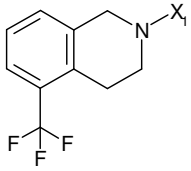
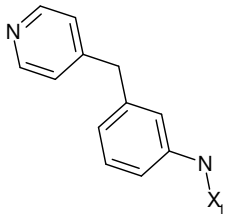
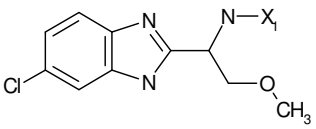
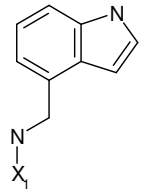
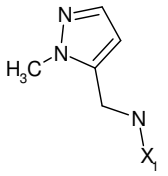
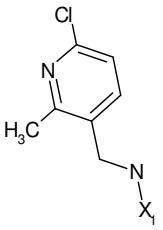
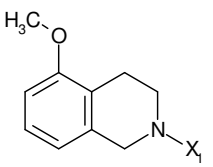
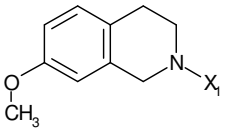
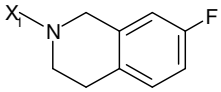
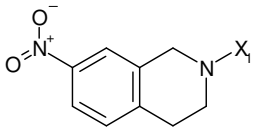
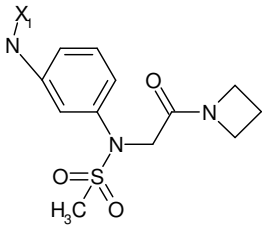
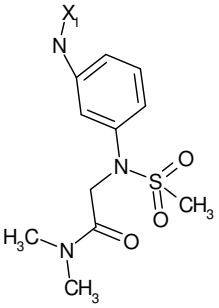
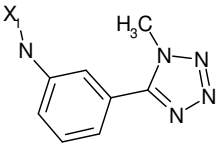
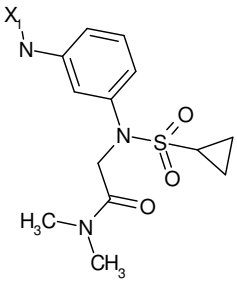
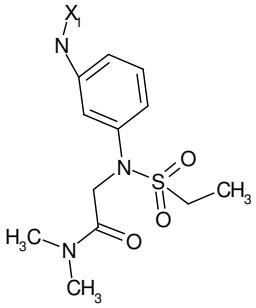
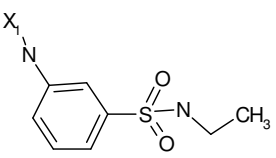
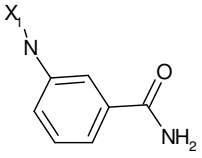
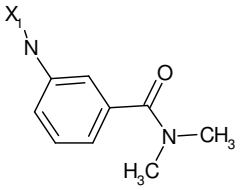
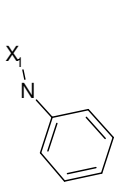
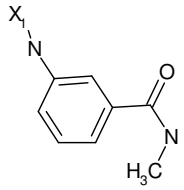
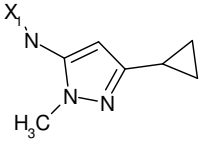
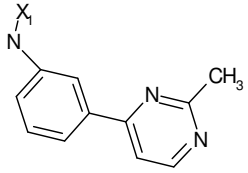
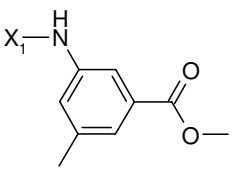
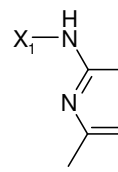
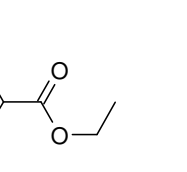
A is CH_2, O or NMe;

R^1 is selected from


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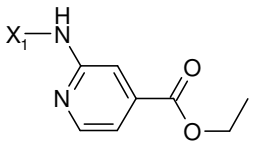
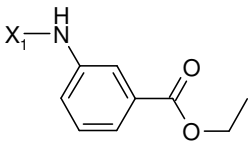
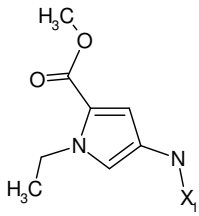
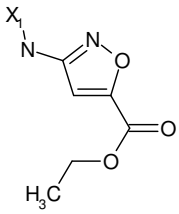
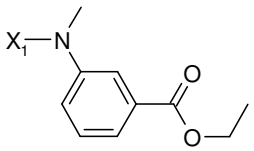
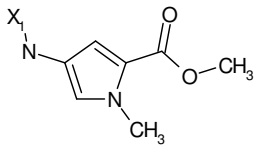
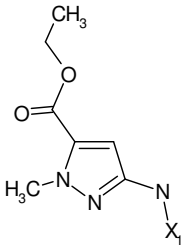
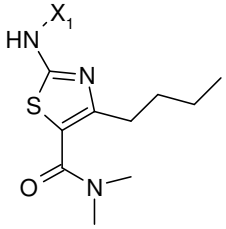
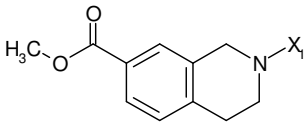
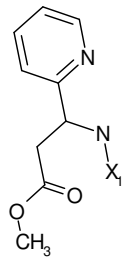
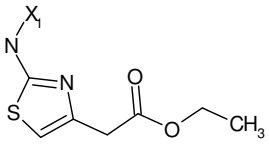
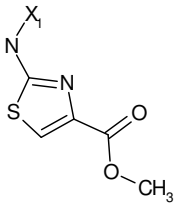
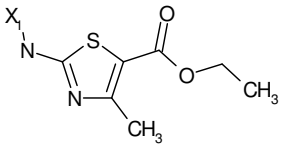
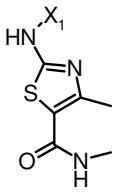
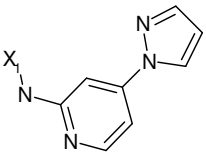
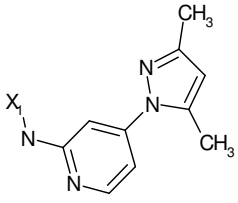
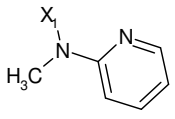
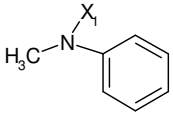
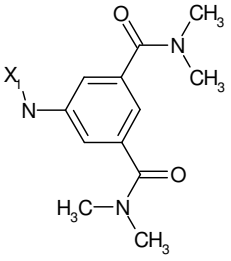
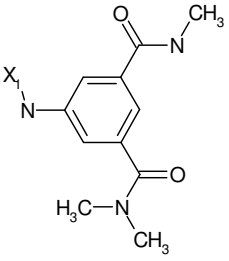
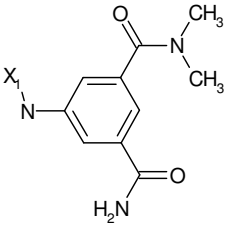
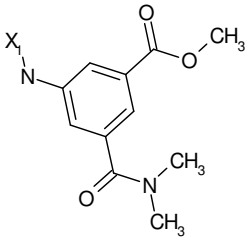
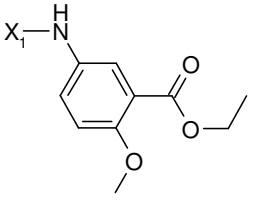
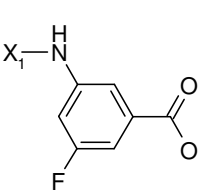
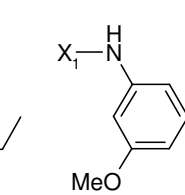
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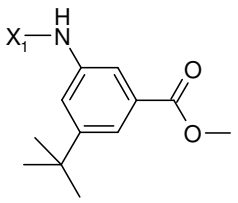
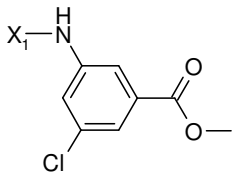
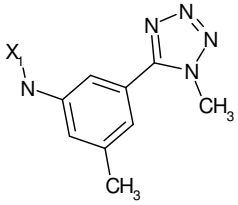
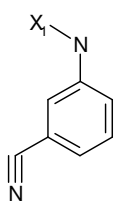
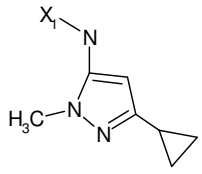
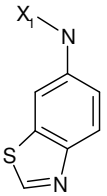
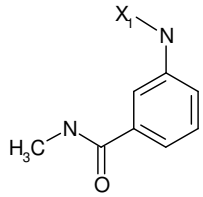
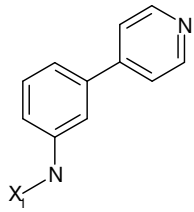
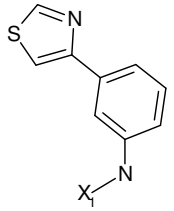
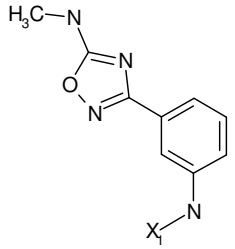
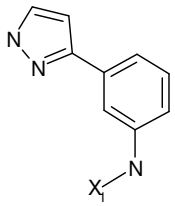
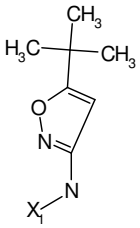
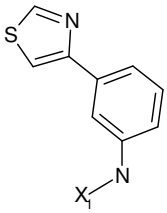
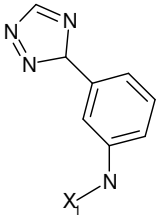
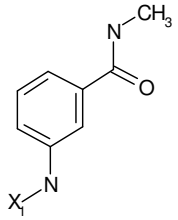
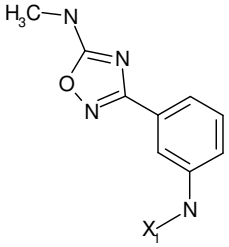
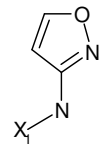
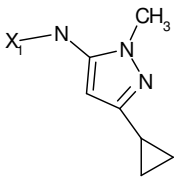
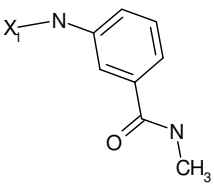
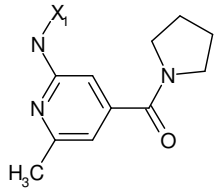
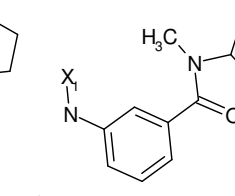
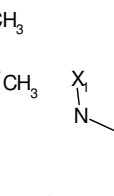
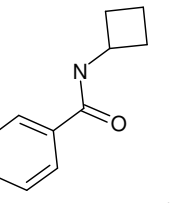
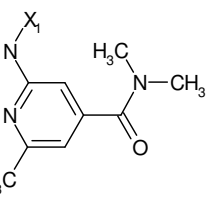
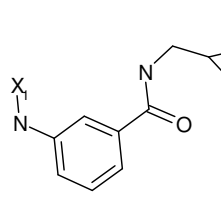
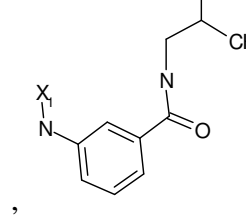
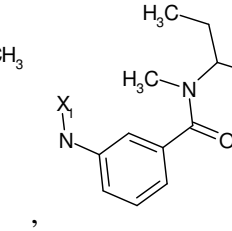
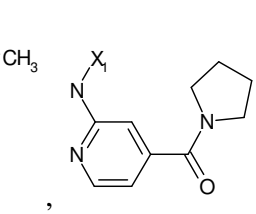

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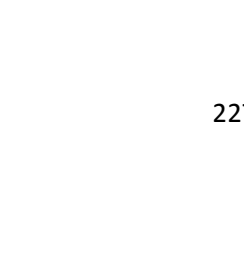
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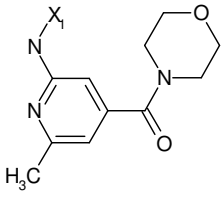
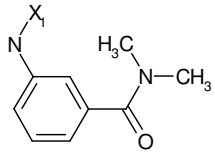
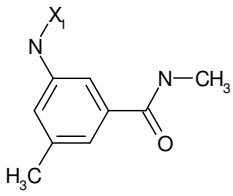
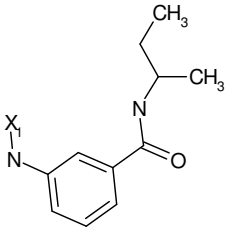
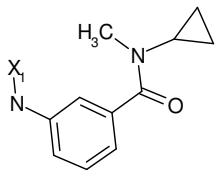
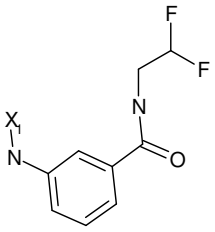
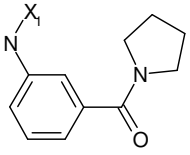
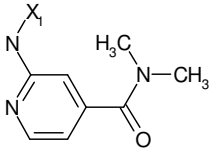
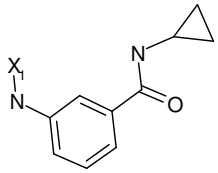
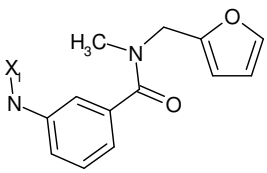
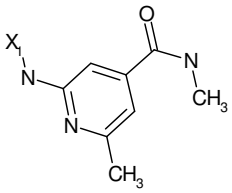
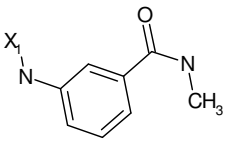
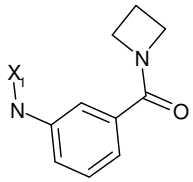
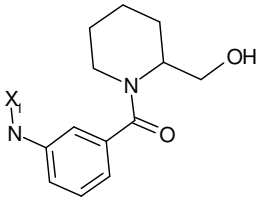
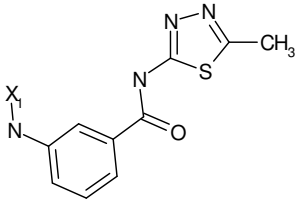
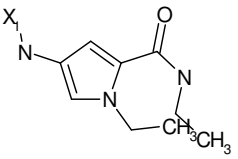
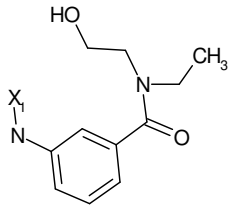
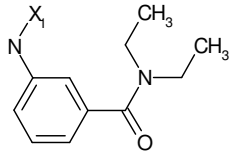
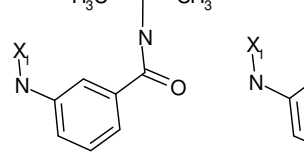
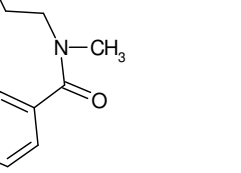
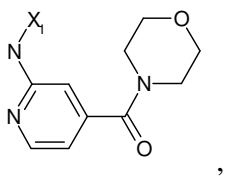
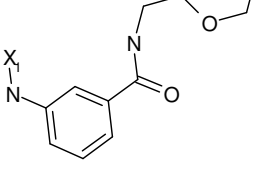
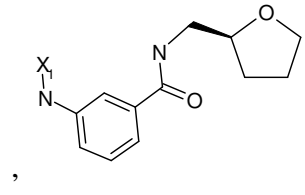
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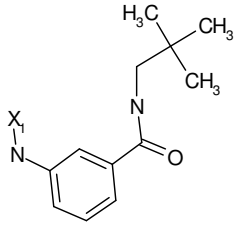
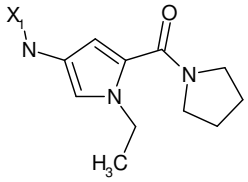
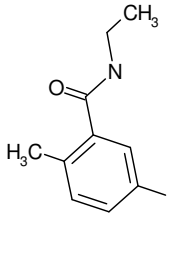
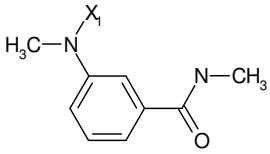
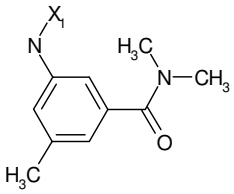
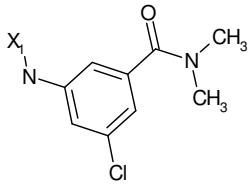
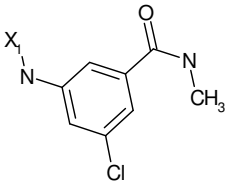
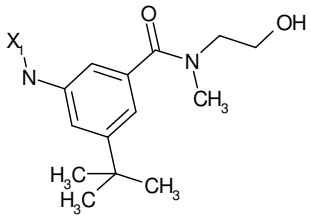
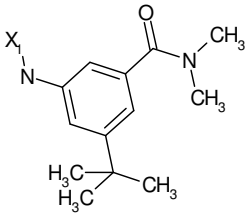
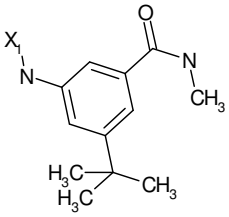
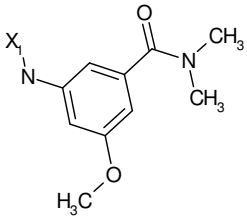
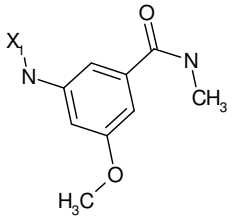
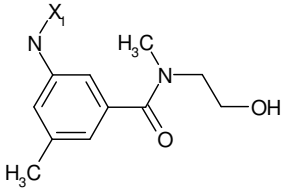
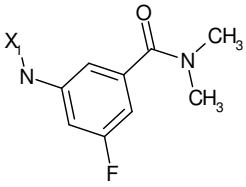
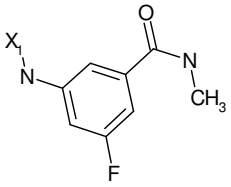
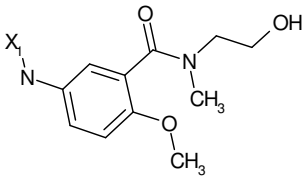
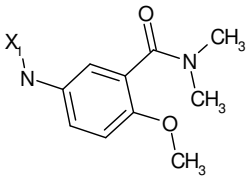
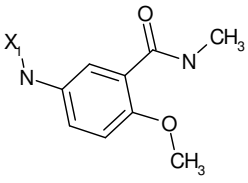
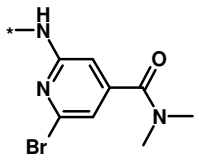
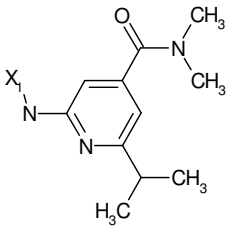
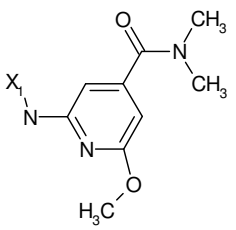
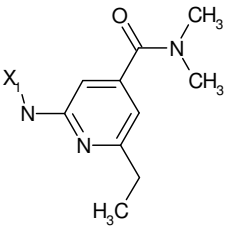
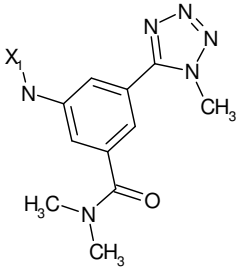
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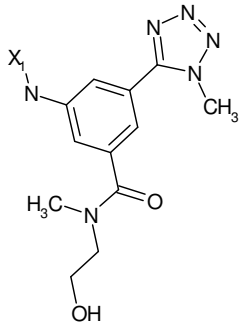
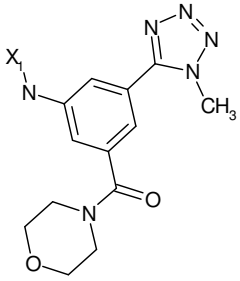
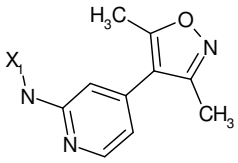
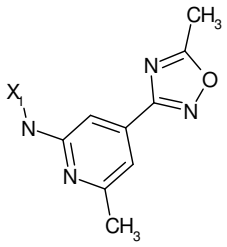
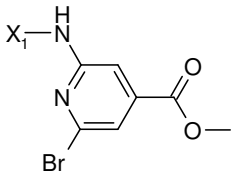
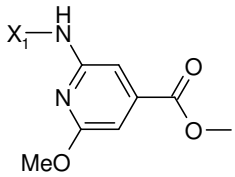
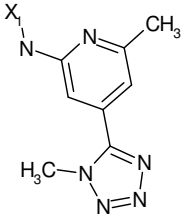
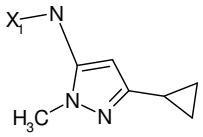
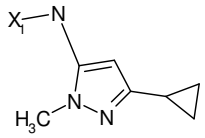
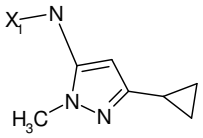
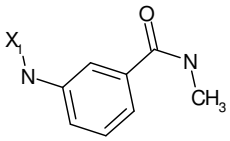
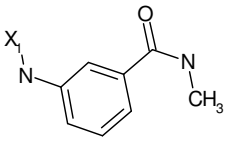
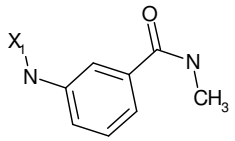
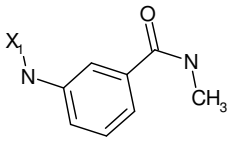
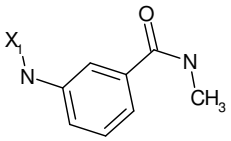
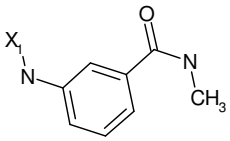
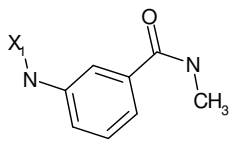
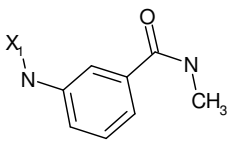
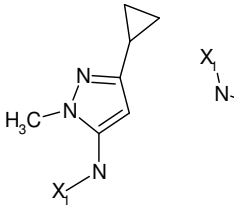
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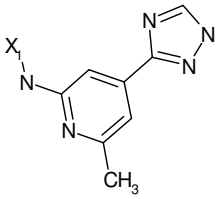
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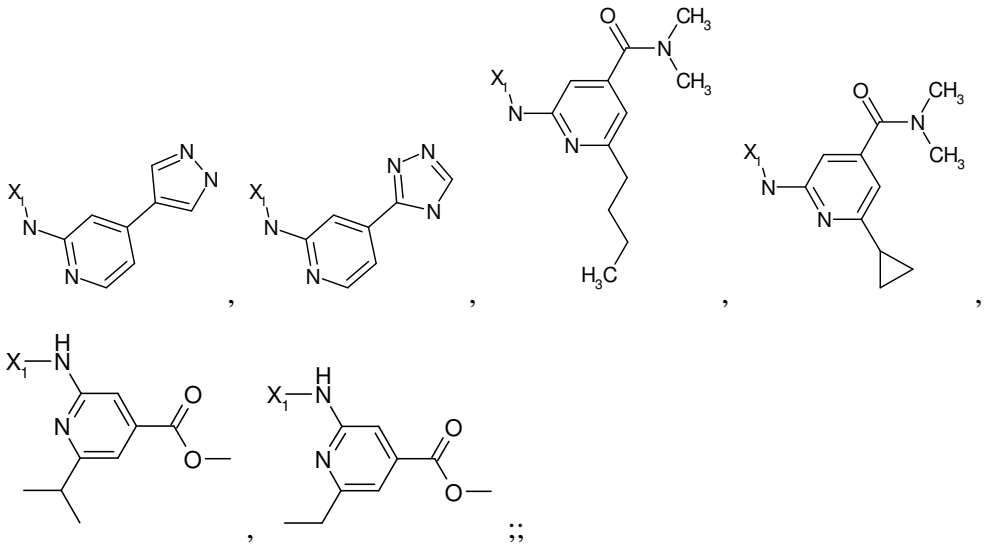

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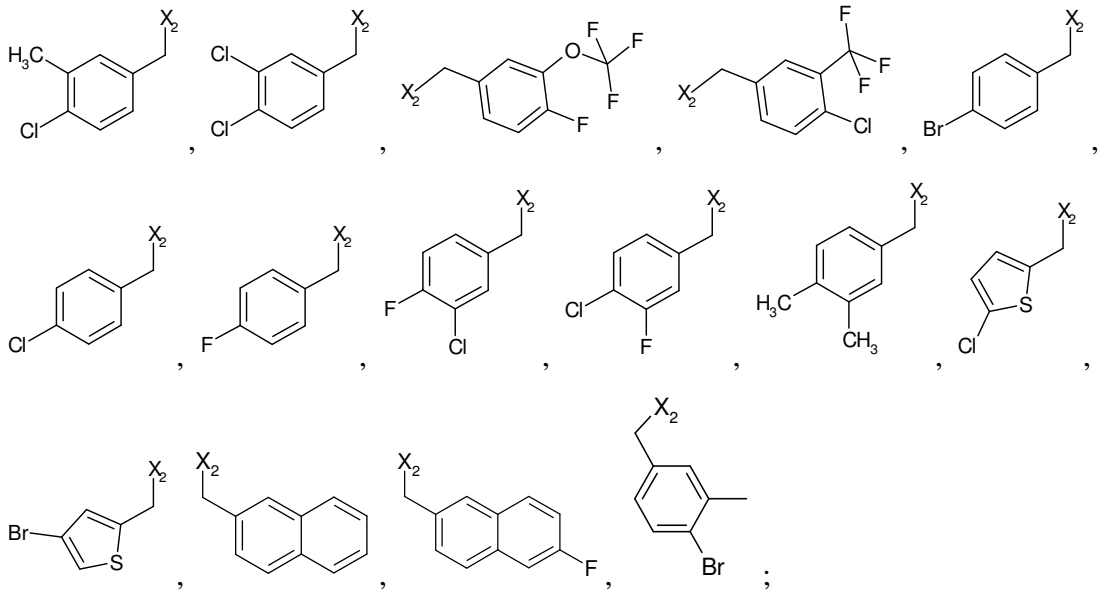
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R^2 is selected from

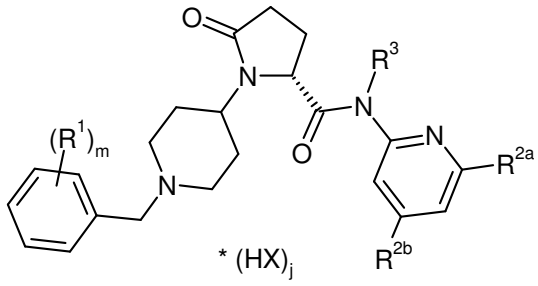


R^3 is H;

R^4 is H;

or **R^3** and **R^4** together are forming a CH_2-CH_2 group.

8. The use of claim 1 or the compound for use of claim 2 wherein the compound is a co-crystal of formula



wherein

R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, halogene;

m is 1, 2 or 3;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, halogene;

$R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl;

$R^{2b.2}$ is H, C_{1-6}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom

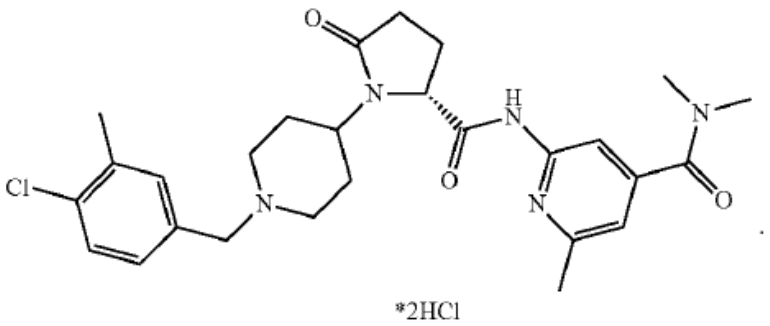
R^3 is H, C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, benzoate, citrate, salicylate, fumarate, tartrate, dibenzoyltartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

j is 0, 0.5, 1, 1.5 or 2;

with a co-crystal former selected from the group consisting of orotic acid, hippuric acid, L-pyroglutamic acid, D-pyroglutamic acid, nicotinic acid, L-(+)-ascorbic acid, saccharin, piperazine, 3-hydroxy-2-naphtoic acid, mucic (galactaric) acid, pamoic (embonic) acid, stearic acid, cholic acid, deoxycholic acid, nicotinamide, isonicotinamide, succinamide, uracil, L-lysine, L-proline, D-valine, L-arginine, glycine.

9. The use of claim 1 or the compound for use of claim 2 wherein the compound is a crystalline salt of the formula below,

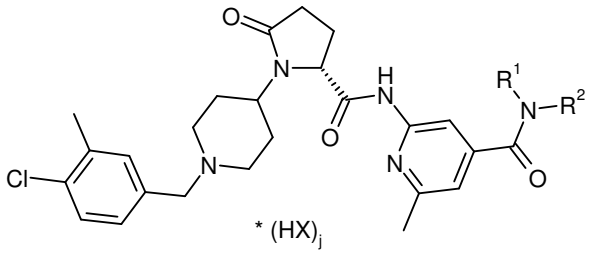


10. The use of claim 1 or the compound for use of claim 2 wherein the compound comprises at least one co-crystal of a compound of the formula according to claim 8 and a pharmaceutically acceptable carrier.

11. The use of claim 1 or the compound for use of claim 2 wherein the compound of formula 1 is to be administered in the form of the individual optical isomers, a mixture

of the individual enantiomers, a racemate or in the form of the enantiomerically pure compounds.

12. The use of claim 1 or the compound for use of claim 2 wherein the compound is a pharmaceutical composition comprising as an active ingredient one or more compounds of the formula below,



1

wherein

R^1 is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, C_{1-6}-haloalkyl;

R^2 is H, C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride or ½ dibenzoyltartrate

j is 1 or 2,

a first diluent, a second diluent, a binder, a disintegrant and a lubricant.

13. The use or the compound for use of claim 12 wherein the pharmaceutical composition further comprises an additional disintegrant.

14. The use or the compound for use of claim 12 or 13 wherein the pharmaceutical composition further comprises an additional glidant.

15. The use or the compound for use of claim 12, 13 or 14 wherein the diluent of the pharmaceutical composition further comprises cellulose powder, dibasic calciumphosphatae anhydrous, dibasic calciumphosphate dehydrate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelantinized starch, or xylitol.

16. The use or the compound for use of any of the preceding claims wherein the neurodegenerative disease is from the group consisting of Alzheimer's disease, Parkinson's disease, frontotemporal dementia, Huntington’s disease, amyotrophic lateral sclerosis, multiple sclerosis, glaucoma, myotonic dystrophy, vascular dementia, progressive supranuclear palsy.