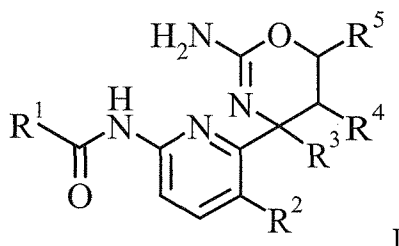


wherein the substituents and variables are as described below and in the claims, or a pharmaceutically acceptable salt thereof.

Hence, in one aspect, there is provided a compound of formula I,



wherein

R¹ is selected from the group consisting of

i) —aryl,

ii) —aryl substituted by 1-4 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl,

iii) i) —heteroaryl, and

iv) ii) —heteroaryl substituted by 1-4 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl;

wherein heteroaryl is pyridinyl, 1H-pyrazolyl or pyrazinyl;

R² is selected from the group consisting of

i) hydrogen,

ii) C₁₋₆-alkyl, and

iii) halogen;

R³ is selected from the group consisting of

i) C₁₋₆-alkyl, and

ii) halogen-C₁₋₆-alkyl,

R⁴ is selected from the group consisting of

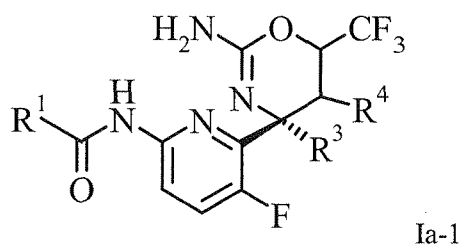
i) halogen, and

ii) hydrogen,

R⁵ is halogen-C₁₋₆-alkyl;

or pharmaceutically acceptable salts thereof.

In another aspect, there is provided a compound of formula I, which is of formula Ia-1



wherein

R¹ is selected from the group consisting of

- i) —aryl,
- ii) —aryl substituted by 1-2 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl,
- iii) —heteroaryl, and
- iv) —heteroaryl substituted by 1-2 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl; wherein heteroaryl is pyridinyl, 1H-pyrazolyl or pyrazinyl; and

R³ is selected from the group consisting of

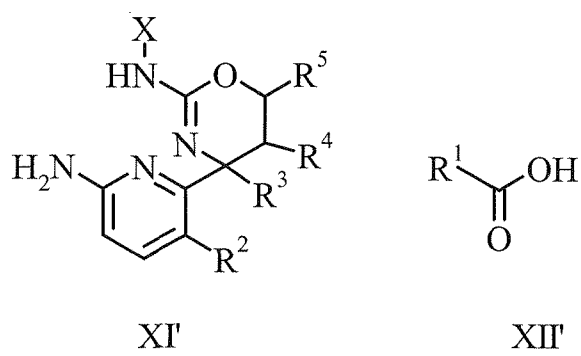
- i) C₁₋₆-alkyl, and
- ii) halogen-C₁₋₆-alkyl,

R⁴ is selected from the group consisting of

- i) halogen, and
- ii) hydrogen,

or pharmaceutically acceptable salts thereof.

In another aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises reacting-contacting a compound of formula XI' with a compound of formula XII' and a condensating agent in the presence of an amine in a solvent at 0°C to ambient temperature to form a compound of formula I



wherein R¹, R², R³, R⁴ and R⁵ are as defined above and X is an amino protecting group.

~~In another aspect, there is provided a compound of formula I as defined above, whenever prepared by a process as defined above.~~

In another aspect, there is provided a compound of formula I as defined above for use as therapeutically active substance.

5 | ____ In another aspect, there is provided a compound of formula I as defined above for the use as therapeutically active substance for the therapeutic and/or prophylactic treatment of diseases and disorders characterized by elevated β -amyloid levels and/or β -amyloid oligomers and/or β -amyloid plaques and further deposits or Alzheimer's disease.

10 | ____ In another aspect, there is provided a compound of formula I as defined above for the use as therapeutically active substance for the therapeutic and/or prophylactic treatment of amyotrophic lateral sclerosis (ALS), arterial thrombosis, autoimmune/inflammatory diseases, cancer such as breast cancer, cardiovascular diseases such as myocardial infarction and stroke, dermatomyositis, Down's Syndrome, gastrointestinal diseases, Glioblastoma multiforme, Graves Disease, Huntington's Disease, inclusion body myositis (IBM), inflammatory reactions, Kaposi Sarcoma, Kostmann Disease, lupus erythematosus, 15 | macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, malignant melanoma, multiple mieloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.

20 | ____ In another aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined above and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.

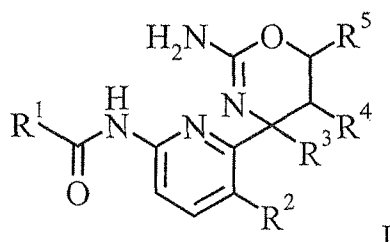
In another aspect, there is provided use of a compound of formula I as defined above for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Alzheimer's disease.

25 | ____ In another aspect, there is provided use of a compound of formula I as defined above for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of amyotrophic lateral sclerosis (ALS), arterial thrombosis, ~~autoimmune/inflammatory diseases, cancer such as breast cancer, cardiovascular diseases such as myocardial infarction and stroke, dermatomyositis, Down's Syndrome, gastrointestinal diseases,~~ Glioblastoma multiforme, Graves Disease, Huntington's Disease, inclusion body myositis (IBM), inflammatory reactions, Kaposi Sarcoma, Kostmann Disease, lupus erythematosus, 30 | macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, malignant melanoma, multiple mieloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.

The present compounds have Asp2 (β -secretase, BACE1 or Memapsin-2) inhibitory activity and may therefore be used in the therapeutic and/or prophylactic treatment of diseases and disorders characterized by elevated β -amyloid levels and/or β -amyloid oligomers and/or 35 | β -amyloid plaques and further deposits, particularly Alzheimer's disease.

Claims

1. A compound of formula I,

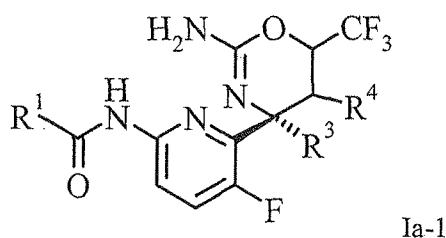


wherein

- 5 R¹ is selected from the group consisting of
- i) —aryl,
 - ii) —aryl substituted by 1-4 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl,
 - 10 iii) i) —heteroaryl, and
 - iv) ii) —heteroaryl substituted by 1-4 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl;
- 15 R² is selected from the group consisting of
- i) hydrogen,
 - ii) C₁₋₆-alkyl, and
 - iii) halogen;
- R³ is selected from the group consisting of
- 20 i) C₁₋₆-alkyl, and
 - ii) halogen-C₁₋₆-alkyl,
- R⁴ is selected from the group consisting of
- i) halogen, and
 - ii) hydrogen,
- 25 R⁵ is halogen-C₁₋₆-alkyl;

or pharmaceutically acceptable salts thereof.

2. A compound of formula I, which is of formula Ia-1



wherein

R¹ is selected from the group consisting of

i) —aryl,

ii) —aryl substituted by 1-2 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl,

iii) i) —heteroaryl, and

iv) ii) —heteroaryl substituted by 1-2 substituents individually selected from amino, cyano, cyano-C₁₋₆-alkyl, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkynyl-C₁₋₆-alkoxy, C₂₋₆-alkynyl and C₁₋₆-alkyl; wherein heteroaryl is pyridinyl, 1H-pyrazolyl or pyrazinyl;

and

R³ is selected from the group consisting of

i) C₁₋₆-alkyl, and

ii) halogen-C₁₋₆-alkyl,

R⁴ is selected from the group consisting of

i) halogen, and

ii) hydrogen,

or pharmaceutically acceptable salts thereof.

3. A compound according to any of claims 1-2, wherein R¹ is pyridinyl, 1H-pyrazolyl or pyrazinyl, ~~heteroaryl~~-substituted by 1-2 substituents individually selected from cyano, halogen, halogen-C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, C₁₋₆-alkoxy and C₁₋₆-alkyl.

4. A compound according to any of claims 1-3, wherein R¹ is ~~heteroaryl~~-pyridinyl, 1H-pyrazolyl or pyrazinyl, substituted by 1-2 substituents individually selected from amino and cyano.

5. A compound according to any of claims 1-4, wherein ~~whenever R¹ is heteroaryl it is~~ pyridinyl, 1H-pyrazolyl or pyrazinyl.

6. A compound according to any of claims 1-5, wherein ~~whenever R¹ is heteroaryl it is~~ pyridinyl or pyrazinyl.

~~7. A compound according to any of claims 1-6, wherein whenever R¹ is heteroaryl it is pyridinyl.~~

~~8-7.~~ A compound according to any of claims 1-~~7~~6, wherein R¹ is 3,5-dichloro-pyridinyl, 3-chloro-5-cyano-pyridinyl, 3-chloro-5-trifluoromethyl-pyridinyl, 4-chloro-1-(difluoromethyl)-1H-pyrazolyl, 5-(difluoromethyl)-pyrazinyl, 5-(fluoromethoxy)pyridinyl, 5-cyano-3-methyl-pyridinyl, 5-cyano-pyridinyl, 5-methoxy-pyrazinyl or 5-methoxy-pyridinyl

~~9-8.~~ A compound according to any of claims 1-~~8~~7, wherein R¹ is 5-cyano-pyridine-2-yl.

- 10.9. A compound according to any of claims 1-98, wherein R² is halogen.
- 11.10. A compound according to any of claims 1-109, wherein R² is F.
- 12.11. A compound according to any of claims 1-110, wherein R³ is C₁₋₆-alkyl.
- 13.12. A compound according to any of claims 1-121, wherein R³ is methyl.
- 5 14.13. A compound according to any of claims 1-131, wherein R⁴ is halogen.
- 15.14. A compound according to any of claims 1-141, wherein R⁴ is fluoro.
- 16.15. A compound according to any of claims 1-151, wherein R⁴ is hydrogen.
- 17.16. A compound according to any of claims 1-161, wherein R⁵ is fluoro-C₁₋₆-alkyl.
- 18.17. A compound according to any of claims 1-171, wherein R⁵ is trifluoromethyl.
- 10 19.18. A compound according to any of claims 1-181, that is selected from the group consisting of

N-(6-((4R,5R,6R)-2-amino-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-cyanopicolinamide,

- 15 N-(6-((4R,5R,6S)-2-amino-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-cyanopicolinamide,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-cyanopicolinamide,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-3-chloro-5-cyanopicolinamide,

- 20 N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide 2,2,2-trifluoroacetate,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-methoxypyrazine-2-carboxamide 2,2,2-trifluoroacetate,

- 25 N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-cyano-3-methylpicolinamide 2,2,2-trifluoroacetate,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-methoxypicolinamide 2,2,2-trifluoroacetate,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate,

N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-(difluoromethyl)pyrazine-2-carboxamide 2,2,2-trifluoroacetate,

5 N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-3,5-dichloropicolinamide 2,2,2-trifluoroacetate,

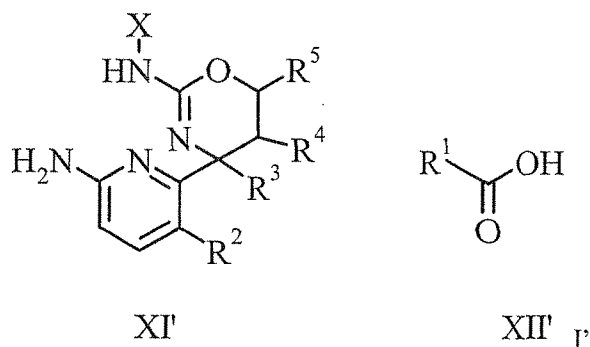
N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-(fluoromethoxy)picolinamide 2,2,2-trifluoroacetate, and

10 N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-chloropyridin-2-yl)-5-cyanopicolinamide,

or pharmaceutically acceptable salts thereof.

20,19. A compound according to any of claims 1-1918, which is N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-cyanopicolinamide or a pharmaceutically acceptable salt thereof.

15 21,20. A process for preparing a compound of formula I as defined in any of claims 1 to 2019, which process comprises ~~reacting~~ contacting a compound of formula XI' with a compound of formula XII' and a condensating agent in the presence of an amine in a solvent at 0°C to ambient temperature to form a compound of formula I



20 wherein R¹, R², R³, R⁴ and R⁵ are as defined in any of claim 1 to 2019 and X is an amino protecting group.

22. A compound of formula I according to any of claims 1-2019, whenever prepared by a process as defined in claim 1720.

25 23,21. A compound of formula I according to any of claims 1-2019 for use as therapeutically active substance.

- 24.22. _____ A compound of formula I according to claims 1-20-19 for the use as therapeutically active substance for the therapeutic and/or prophylactic treatment of diseases and disorders characterized by elevated β -amyloid levels and/or β -amyloid oligomers and/or β -amyloid plaques and further deposits or Alzheimer's disease.
- 5 | 25.23. _____ A compound of formula I according to claims 1-20-19 for the use as therapeutically active substance for the therapeutic and/or prophylactic treatment of amyotrophic lateral sclerosis (ALS), arterial thrombosis, autoimmune/inflammatory diseases, cancer such as breast cancer, cardiovascular diseases such as myocardial infarction and stroke, dermatomyositis, Down's Syndrome, gastrointestinal diseases, Glioblastoma multiforme, Graves Disease, Huntington's Disease, inclusion body myositis (IBM), inflammatory reactions, Kaposi Sarcoma, Kostmann Disease, lupus erythematosus, macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, malignant melanoma, multiple mieloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.
- 10 |
- 15 | 26.24. _____ A pharmaceutical composition comprising a compound of formula I according to any of claims 1-20-19 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.
- 27.25. _____ Use of a compound of formula I according to any of claims 1-20-19 for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Alzheimer's disease.
- 20 |
- 25 | 28.26. _____ Use of a compound of formula I according to any of claims 1-20-19 for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of amyotrophic lateral sclerosis (ALS), arterial thrombosis, ~~autoimmune/inflammatory diseases~~, cancer such as breast cancer, ~~cardiovascular diseases such as myocardial infarction and stroke~~, dermatomyositis, Down's Syndrome, ~~gastrointestinal diseases~~, Glioblastoma multiforme, Graves Disease, Huntington's Disease, inclusion body myositis (IBM), inflammatory reactions, Kaposi Sarcoma, Kostmann Disease, lupus erythematosus, macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, malignant melanoma, multiple mieloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.
- 30 |
- 35 | 29. ~~A method for the use in the therapeutic and/or prophylactic treatment of Alzheimer's disease or amyotrophic lateral sclerosis (ALS), arterial thrombosis, autoimmune/inflammatory diseases, cancer such as breast cancer, cardiovascular diseases such as myocardial infarction and stroke, dermatomyositis, Down's Syndrome, gastrointestinal diseases, Glioblastoma multiforme, Graves Disease, Huntington's Disease, inclusion body myositis (IBM), inflammatory reactions, Kaposi Sarcoma, Kostmann Disease, lupus erythematosus, macrophagic myofasciitis, juvenile idiopathic arthritis,~~

~~granulomatous arthritis, malignant melanoma, multiple myeloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease, which method comprises administering a compound of formula I according to any of claims 1-20 to a human being or animal.~~