

Jul;26(13):4970-81), Macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, Breast cancer (Hedlund M. *et al*, Cancer Res. 2008 Jan 15;68(2):388-94 and Kondoh K. *et al.*, Breast Cancer Res Treat. 2003 Mar;78(1):37-44), Gastrointestinal diseases (Hoffmeister A. *et al*, JOP. 2009 Sep 4;10(5):501-6), Autoimmune/inflammatory diseases (Woodard-Grice A.V. *et al.*, J Biol Chem. 2008 Sep 26;283(39):26364-73. Epub 2008 Jul 23), Rheumatoid Arthritis (Toegel S. *et al*, Osteoarthritis Cartilage. 2010 Feb;18(2):240-8. Epub 2009 Sep 22), Inflammatory reactions (Lichtenthaler S.F. *et al.*, J Biol Chem. 2003 Dec 5;278(49):48713-9. Epub 2003 Sep 24), Arterial Thrombosis (Merten M. *et al.*, Z Kardiol. 2004 Nov;93(11):855-63), Cardiovascular diseases such as Myocardial infarction and stroke (Maugeri N. *et al.*, Srp Arh Celok Lek. 2010 Jan;138 Suppl 1:50-2) and Graves disease (Kiljański J. *et al*, Thyroid. 2005 Jul;15(7):645-52).

WO2013027188 describe 2-Amino-4-(pyridin-2-yl)-5,6-dihydro-4H-1,3-oxazine derivatives and their use as BACE-1 and/or BACE- 2 inhibitors, EP2511268 and WO012147763 describe oxazine derivatives as BACE1 inhibitors.

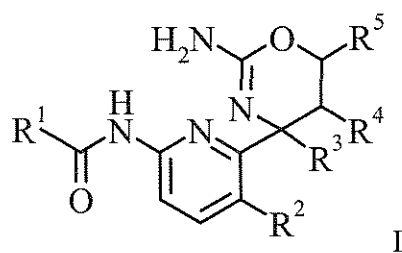
15 The present invention provides novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as Alzheimer's disease. Furthermore the use of compounds of formula I in the treatment of amyotrophic lateral sclerosis (ALS), arterial thrombosis, autoimmune/inflammatory diseases, 20 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, 25 Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease and Wilson's Disease. The novel compounds of formula I have improved pharmacological properties.

Field of the Invention

30 The present invention provides Fluoromethyl-5,6-dihydro-4H-[1,3]oxazin-2-ylamines having BACE1 inhibitory properties, their manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

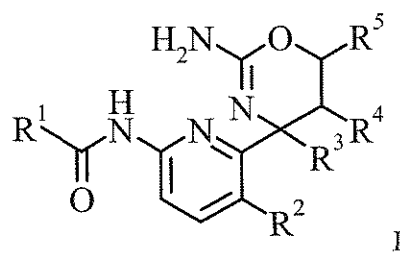
Summary of the Invention

The present invention ~~disclosure~~ provides a compound of formula I,



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

R^1 is selected from the group consisting of

i) aryl,

ii) aryl substituted by 1-4 substituents individually selected from amino, cyano, cyano- C_{1-6} -alkyl, halogen, halogen- C_{1-6} -alkoxy, halogen- C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, C_{2-6} -alkynyl- C_{1-6} -alkoxy, C_{2-6} -alkynyl and C_{1-6} -alkyl,

iii) heteroaryl, and

iv) heteroaryl substituted by 1-4 substituents individually selected from amino, cyano, cyano- C_{1-6} -alkyl, halogen, halogen- C_{1-6} -alkoxy, halogen- C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, C_{2-6} -alkynyl- C_{1-6} -alkoxy, C_{2-6} -alkynyl and C_{1-6} -alkyl;

R^2 is selected from the group consisting of

i) hydrogen,

ii) C_{1-6} -alkyl, and

iii) halogen;

R^3 is selected from the group consisting of

i) C_{1-6} -alkyl, and

ii) halogen- C_{1-6} -alkyl,

R^4 is selected from the group consisting of

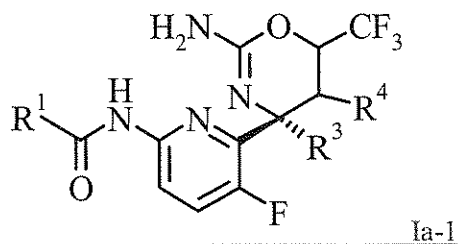
i) halogen, and

ii) hydrogen,

R^5 is halogen- C_{1-6} -alkyl;

or pharmaceutically acceptable salts thereof.

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



wherein

R^1 is selected from the group consisting of

- 5 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
 10 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; and

R^3 is selected from the group consisting of

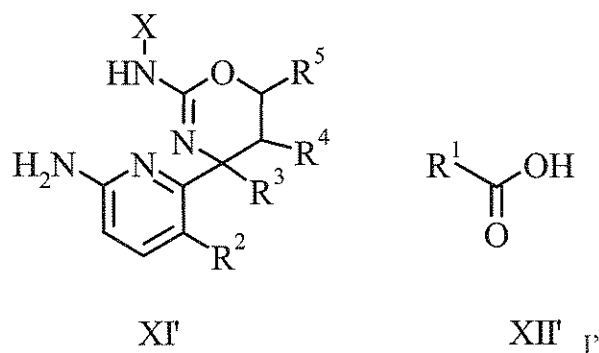
- 15 i) C₁₋₆-alkyl, and
 ii) halogen-C₁₋₆-alkyl.

R^4 is selected from the group consisting of

- i) halogen, and
- ii) hydrogen,

or pharmaceutically acceptable salts thereof.

- 20 In another aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises reacting a compound of formula XI' with a compound of formula XII' to a compound of formula I



wherein R^1 , R^2 , R^3 , R^4 and R^5 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 myeloma, 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.

_____ 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
25 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 myeloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.

35 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 β -amyloid plaques and further deposits, particularly Alzheimer's disease.

Detailed Description of the Invention

The present invention provides a compound of formula I and their pharmaceutically acceptable salts thereof, the preparation of the above mentioned compounds, medicaments containing them and their manufacture as well as the use of the above mentioned compounds in the therapeutic and/or prophylactic treatment of diseases and disorders which are associated with inhibition of BACE1, such as Alzheimer's disease. Furthermore, the formation, or formation and deposition, of β -amyloid plaques in, on or around neurological tissue (e.g., the brain) are inhibited by the present compounds by inhibiting the A β production from APP or an APP fragment.

The following definitions of the general terms used in the present description apply irrespectively of whether the terms in question appear alone or in combination with other groups.

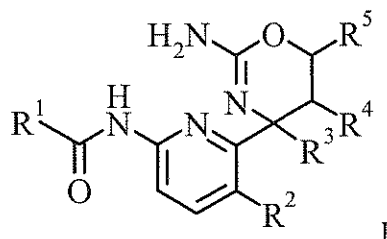
Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

The term "C₁₋₆-alkyl", alone or in combination with other groups, stands for a hydrocarbon radical which may be linear or branched, with single or multiple branching, wherein the alkyl group in general comprises 1 to 6 carbon atoms, for example, methyl (Me), ethyl (Et), propyl, isopropyl (i-propyl), n-butyl, i-butyl (isobutyl), 2-butyl (sec-butyl), t-butyl (*tert*-butyl), isopentyl, 2-ethyl-propyl (2-methyl-propyl), 1,2-dimethyl-propyl and the like. Particular "C₁₋₆-alkyl" are "C₁₋₃-alkyl". Specific groups are methyl and ethyl. Most specific is methyl.

The term "halogen-C₁₋₆-alkyl", alone or in combination with other groups, refers to C₁₋₆-alkyl as defined herein, which is substituted by one or multiple halogen, particularly 1-5 halogen,

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) heteroaryl, and
- iv) 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;

R² is selected from the group consisting of

- 15
- 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,

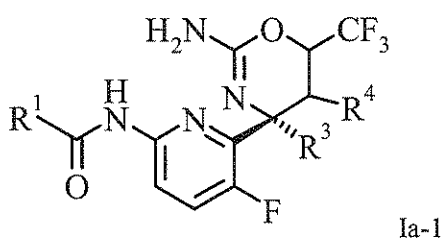
R⁴ is selected from the group consisting of

- i) halogen, and
- ii) hydrogen,

R⁵ is halogen-C₁₋₆-alkyl;

25 or pharmaceutically acceptable salts thereof.

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



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,

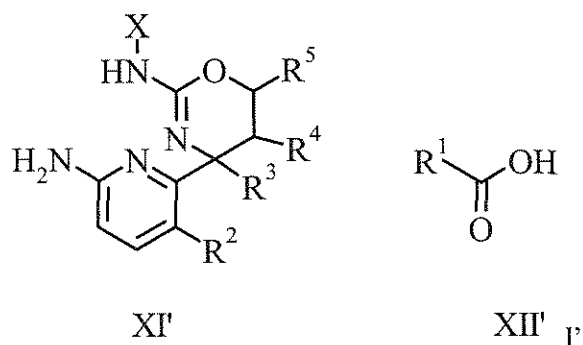
N-(6-((4S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-5-fluoropyridin-2-yl)-5-(fluoromethoxy)picolinamide 2,2,2-trifluoroacetate, and

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. A compound according to any of claims 1-19, 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. A process for preparing a compound of formula I as defined in any of claims 1 to 20, which process comprises reacting a compound of formula XI' with a compound of formula XII' to a compound of formula I:



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

20 22. A compound of formula I according to any of claims 1-20, whenever prepared by a process as defined in claim 17.

23. A compound of formula I according to any of claims 1-20 for use as therapeutically active substance.