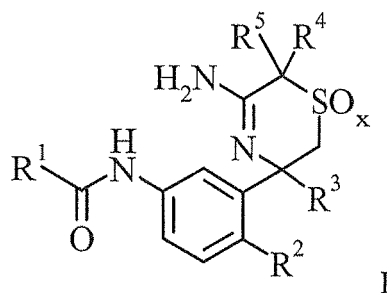
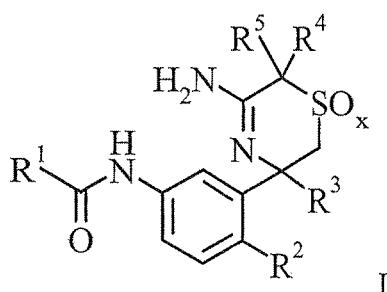


The present disclosure provides a compound of formula I,



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

5 In a first aspect, there is provided a compound of formula I,



wherein

R¹ is selected from the group consisting of

i) ~~aryl,~~

10 ii) ~~aryl substituted by 1-4 substituents individually selected from 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~~

15 iv) ~~heteroaryl substituted by 1-4 substituents individually selected from 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~~
5-cyano-pyridine-2-yl, 5-chloro-pyridine-2-yl, 5-difluoromethoxy-pyridine-2-yl, 5-methoxy-pyrazine-2-yl or 5-difluoromethyl-pyrazine-2-yl;

R² is selected from the group consisting of

20 i) ~~hydrogen,~~

ii) ~~C₁-₆-alkyl, and~~

iii) ~~halogenF;~~

R³ is selected from the group consisting of

i) ~~C₁-₆-alkyl, and~~

25 ii) ~~halogen-C₁-₆-alkyl~~methyl,

R⁴ is selected from the group consisting of

- i) C_{1-6} -alkylmethyl, and
- ii) —halogen- C_{1-6} -alkyl, and
- iii) ii) hydrogen,

R^5 is selected from the group consisting of

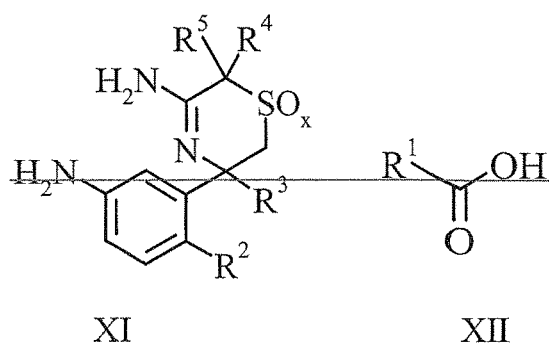
- i) C_{1-6} -alkylmethyl, and
- ii) —halogen- C_{1-6} -alkyl, and
- iii) ii) hydrogen,

or R^4 and R^5 together form a C_{3-7} -cycloalkyl ring, optionally substituted by one or more halogen,

x is 0 or 2,

or pharmaceutically acceptable salts thereof.

~~In a second aspect, there is provided a process for preparing a compound of formula I as defined herein, which process comprises reacting a compound of formula XI with a compound of formula XII to a compound of formula I~~



wherein x , R^1 , R^2 , R^3 , R^4 and R^5 are as defined herein.

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

~~In a fourth aspect, there is provided a compound of formula I as defined herein for use as therapeutically active substance.~~

~~In a fifth aspect, there is provided a compound of formula I as defined herein 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.~~

~~In a sixth-second aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined herein and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.~~

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

5 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

10 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
15 inhibited by the present compounds by inhibiting the A β production from APP or an APP fragment.

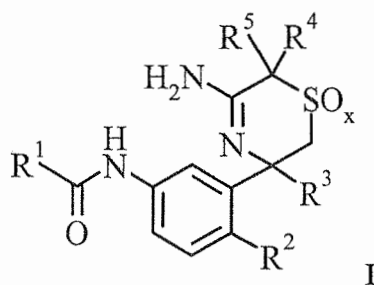
The following definitions of the general terms used in the present description apply irrespectively of whether the terms in question appear alone or in combination with other groups.

20 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.

25 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, 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.

Claims

1. 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 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 1-4 substituents individually selected from 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~~ 5-cyano-pyridine-2-yl, 5-chloro-pyridine-2-yl, 5-difluoromethoxy-pyridine-2-yl, 5-methoxy-pyrazine-2-yl or 5-difluoromethyl-pyrazine-2-yl;

R² is selected from the group consisting of

i) ~~hydrogen,~~

ii) ~~C₁₋₆-alkyl, and~~

iii) ~~halogenF;~~

R³ is selected from the group consisting of

i) ~~C₁₋₆-alkyl, and~~

ii) ~~halogen-C₁₋₆-alkyl, methyl;~~

R⁴ is selected from the group consisting of

i) ~~C₁₋₆-alkyl, methyl, and~~

ii) ~~halogen-C₁₋₆-alkyl, and~~

~~iii) ii) hydrogen,~~

R⁵ is selected from the group consisting of

i) ~~C₁₋₆-alkyl, methyl, and~~

ii) ~~halogen-C₁₋₆-alkyl, and~~

~~iii) ii) hydrogen,~~

or R⁴ and R⁵ together form a C₃₋₇-cycloalkyl ring, optionally substituted by one or more halogen,

| x is 0 or 2,

or pharmaceutically acceptable salts thereof.

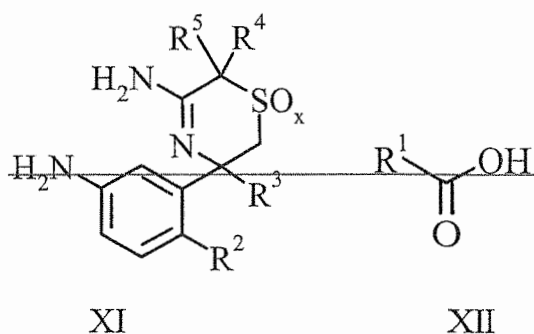
- ~~2. A compound according to claim 1, wherein R² is halogen.~~
- ~~3. A compound according to any of claims 1-2, wherein R² is F.~~
- ~~4. A compound according to any of claims 1-3, wherein R³ is C₁₋₆-alkyl.~~
- ~~5. A compound according to any of claims 1-4, wherein R³ is methyl.~~
- 5 ~~6. A compound according to any of claims 1-5, wherein R⁴ is C₁₋₆-alkyl.~~
- ~~7.2. A compound according to any of claims 1-6, wherein R⁴ is methyl.~~
- ~~8.3. A compound according to any of claims 1-5, wherein R⁴ is hydrogen.~~
- ~~9. A compound according to any of claims 1-8, wherein R⁵ is C₁₋₆-alkyl.~~
- ~~10.4. A compound according to any of claims 1-9, wherein R⁵ is methyl.~~
- 10 ~~11.5. A compound according to any of claims 1-8, wherein R⁵ is hydrogen.~~
- ~~12.6. A compound according to any of claims 1-5, wherein R⁴ and R⁵ together form a C₃₋₇-cycloalkyl ring.~~
- ~~13. A compound according to claim 12, wherein R⁴ and R⁵ together form a cyclobutyl or cyclopentyl ring.~~
- 15 ~~14. A compound according to any of claims 1-13, wherein R¹ is heteroaryl substituted by one substituent individually selected from cyano, halogen, halogen-C₁₋₆-alkyl, halogen-C₁₋₆-alkoxy and C₁₋₆-alkoxy.~~
- ~~15. A compound according to any of claims 1-14, wherein R¹ is 5-cyano-pyridine-2-yl, 5-chloro-pyridine-2-yl, 5-difluoromethoxy-pyridine-2-yl, 5-methoxy-pyrazine-2-yl or 5-difluoromethyl-pyrazine-2-yl.~~
- 20 ~~16. A compound according to any of claims 1-15, wherein x is 2.~~
- ~~17.7. A compound according to any of claims 1-16, selected from the group consisting of~~
5-Cyano-pyridine-2-carboxylic acid [3-((R)-5-amino-3-methyl-3,6-dihydro-2H-[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
25 5-Difluoromethoxy-pyridine-2-carboxylic acid [3-((R)-5-amino-3-methyl-1,1-dioxo-1,2,3,6-tetrahydro-1λ⁶-[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
5-Chloro-pyridine-2-carboxylic acid [3-((R)-5-amino-3,6,6-trimethyl-1,1-dioxo-1,2,3,6-tetrahydro-1λ⁶-[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,

- 5-Cyano-pyridine-2-carboxylic acid [3-((R)-5-amino-3,6,6-trimethyl-1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
- 5-Methoxy-pyrazine-2-carboxylic acid [3-((R)-5-amino-3,6,6-trimethyl-1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
- 5 5-Difluoromethyl-pyrazine-2-carboxylic acid [3-((R)-5-amino-3,6,6-trimethyl-1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
- 5-Cyano-pyridine-2-carboxylic acid [3-((R)-5-amino-3-methyl-1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
- 5-Chloro-pyridine-2-carboxylic acid [3-((R)-5-amino-3-methyl-1,1-dioxo-1,2,3,6-tetrahydro-1 λ^6 -[1,4]thiazin-3-yl)-4-fluoro-phenyl]-amide,
- 10 5-Cyano-pyridine-2-carboxylic acid [3-((R)-9-amino-7-methyl-5,5-dioxo-5 λ^6 -thia-8-aza-spiro[3.5]non-8-en-7-yl)-4-fluoro-phenyl]-amide,
- 5-Chloro-pyridine-2-carboxylic acid [3-((R)-9-amino-7-methyl-5,5-dioxo-5 λ^6 -thia-8-aza-spiro[3.5]non-8-en-7-yl)-4-fluoro-phenyl]-amide, and
- 15 5-Cyano-pyridine-2-carboxylic acid [3-((R)-10-amino-8-methyl-6,6-dioxo-6 λ^6 -thia-9-aza-spiro[4.5]dec-9-en-8-yl)-4-fluoro-phenyl]-amide,

or a pharmaceutical acceptable salt thereof.

20

~~18. A process for preparing a compound of formula I as defined in any of claims 1 to 16, which process comprises reacting a compound of formula XI with a compound of formula XII to a compound of formula I~~



~~wherein x, R¹, R², R³, R⁴ and R⁵ are as defined in any of claim 1 to 16.~~

- ~~19. A compound of formula I according to any of claims 1-17, whenever prepared by a process as defined in claim 18.~~
- ~~20. A compound of formula I according to any of claims 1-17 for use as therapeutically active substance.~~

21. ~~A compound of formula I according to claims 1-17 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 ~~22.8.~~ A pharmaceutical composition comprising a compound of formula I according to any of claims 1-~~17~~-7 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.

23. ~~Use of a compound of formula I according to any of claims 1-17 for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Alzheimer's disease.~~

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