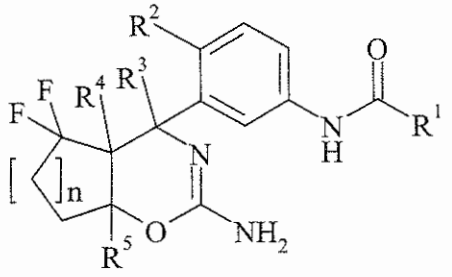
and disorders characterized by elevated β-amyloid levels and/or β-amyloid oligomers and/or β-amyloid plaques and further deposits, particularly Alzheimer's disease.

Summary

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



I

wherein

R^1 is selected from the group consisting of

i) aryl,

ii) aryl substituted by 1-4 substituents individually selected from 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 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) hydrogen, and

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

R^5 is selected from the group consisting of

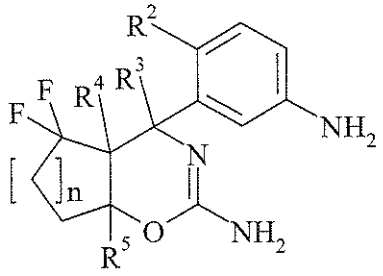
i) hydrogen, and

ii) C_{1-6}-alkyl;

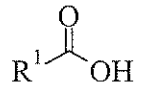
n is 1 or 2;

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 I' with a compound of formula XIV.



I'



XIV

wherein n, R^1, R^2, R^3, R^4, 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, particularly Alzheimer's disease.

In a sixth 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 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

Object of the present invention is 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 activity, 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 Aβ 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.

The term "C_{1-6}-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 contains 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 "C_{1-6}-alkyl" are groups with 1 to 5 carbon atoms. Specific groups are methyl, ethyl and t-butyl. Most specific group is methyl.

The term "cyano-C_{1-6}-alkyl", alone or in combination with other groups, refers to C_{1-6}-alkyl as defined herein, which is substituted by one or multiple cyano, in particular 1-5 cyano, more particular 1 cyano. Examples are cyano-methyl and the like.

The term "halogen-C_{1-6}-alkyl", alone or in combination with other groups, refers to C_{1-6}-alkyl as defined herein, which is substituted by one or multiple halogen, in particular 1-5 halogen, more particular 1-3 halogen, most particular 1 halogen or 3 halogen. Particular halogen is fluoro. Examples are difluoromethyl, chloromethyl, fluoromethyl and the like. A specific group is $-CH_2F$.

The term "C_{1-6}-alkoxy-C_{1-6}-alkyl", alone or in combination with other groups, refers to C_{1-6}-alkyl, which is substituted by one or multiple C_{1-6}-alkoxy as defined herein. Examples are MeO-Me, 1MeO-Et, 2MeO-Et, 1MeO-2EtO-propyl and the like.

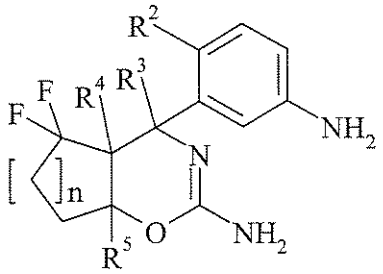
The term "cyano", alone or in combination with other groups, refers to N≡C-(NC-).

The term "halogen", alone or in combination with other groups, denotes chloro (Cl), iodo (I), fluoro (F) and bromo (Br). Particular "halogen" is Cl and F.

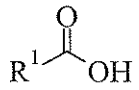
5-Cyano-pyridine-2-carboxylic acid [3-((4S,4aR,8aR)-2-amino-5,5-difluoro-4-methyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e][1,3]oxazin-4-yl)-4-fluoro-phenyl]-amide,
5-Chloro-thiophene-2-carboxylic acid [3-((4S,4aR,8aR)-2-amino-5,5-difluoro-4-methyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e][1,3]oxazin-4-yl)-4-fluoro-phenyl]-amide, and
5-(1,1-Difluoro-ethyl)-pyrazine-2-carboxylic acid [3-((4S,4aR,7aR)-2-amino-5,5-difluoro-4-methyl-4,4a,5,6,7,7a-hexahydro-cyclopenta[e][1,3]oxazin-4-yl)-4-fluoro-phenyl]-amide,

or a pharmaceutical acceptable salt thereof.

14. A process for preparing a compound of formula I as defined in any of claims 1 to 13, which process comprises reacting a compound of formula I' with a compound of formula XIV.



I'



XIV

wherein n, R^1, R^2, R^3, R^4, R^5 are as defined in any of claim 1 to 12.

15. A compound of formula I according to any of claims 1 to 13, whenever prepared by a process as defined in claim 14.

16. A compound of formula I according to any of claims 1 to 13 for use as therapeutically active substance.

17. A compound of formula I according to claims 1 to 13 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, particularly Alzheimer's disease.

18. A pharmaceutical composition comprising a compound of formula I according to any of claims 1 to 13 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.

19. Use of a compound of formula I according to any of claims 1 to 13 for the manufacture of a medicament 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, particularly Alzheimer's disease.

~~20. A method for the use in inhibition of BACE1 activity, particularly 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, which method comprises administering a compound of formula I according to any of claims 1 to 13 to a human being or animal.~~

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