

APP-cleaving enzyme) is an aspartyl protease which is anchored into the membrane by a transmembrane domain (Vassar et al., Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, *Science*. 1999 Oct 22;286(5440):735). It is expressed in many tissues of the human organism but its level is especially high in the CNS.

- 5 Genetic ablation of the BACE1 gene in mice has clearly shown that its activity is essential for the processing of APP which leads to the generation of A $\beta$ -peptides, in the absence of BACE1 no A $\beta$ -peptides are produced (Luo et al., Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation, *Nat Neurosci*. 2001 Mar;4(3):231-2, Roberds et al., BACE knockout mice are healthy despite lacking the primary
- 10 beta-secretase activity in brain: implications for Alzheimer's disease therapeutics, *Hum Mol Genet*. 2001 Jun 1;10(12):1317-24). Mice which have been genetically engineered to express the human APP gene and which form extensive amyloid plaques and Alzheimer's disease like pathologies during aging fail to do so when  $\beta$ -secretase activity is reduced by genetic ablation of one of the BACE1 alleles (McConlogue et al., Partial reduction of BACE1 has dramatic effects
- 15 on Alzheimer plaque and synaptic pathology in APP Transgenic Mice. *J Biol Chem*. 2007 Sep 7;282(36):26326). It is thus presumed that inhibitors of BACE1 activity can be useful agents for therapeutic intervention in Alzheimer's disease (AD).

- Furthermore, the formation, or formation and deposition, of  $\beta$ -amyloid peptides in, on or around neurological tissue (e.g., the brain) are inhibited by the present compounds, i.e. inhibition
- 20 of the A $\beta$ -production from APP or an APP fragment.

- WO2012139425 describes iminothiazine compounds and mono- and dioxides as BACE1 inhibitors. WO2011020806 describes 3-Amino-5-phenyl-5,6-dihydro-2H-[1,4]oxazines as BACE1 inhibitors. WO2011069934 describes 2-Amino-5,5-difluoro-5,6-dihydro-4H-[1,3]oxazin-4-yl)-phenyl]-amide as BACE1 inhibitors. WO2011029803 describes the use of
- 25 aminodihydrothiazine derivatives for the treatment or prevention of metabolic diseases such as preferably diabetes, particularly type 2 diabetes. The compounds are BACE2 inhibitors.

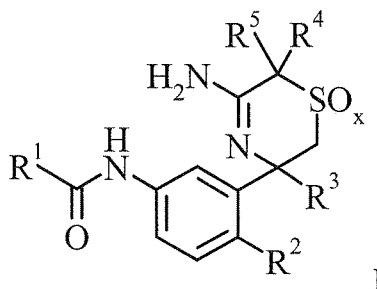
- The present invention provides novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as
- 30 Alzheimer's disease. The novel compounds of formula I have improved pharmacological properties.

### **Field of the Invention**

- The present invention provides 5-amino-[1,4]thiazines having BACE1 inhibitory properties, their manufacture, pharmaceutical compositions containing them and their use as therapeutically
- 35 active substances.

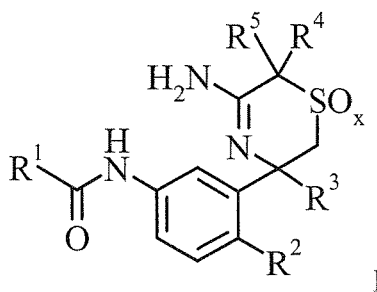
### **Summary of the Invention**

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.

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-C<sub>1-6</sub>-alkyl, halogen, halogen-C<sub>1-6</sub>-alkoxy, halogen-C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkoxy-C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkynyl-C<sub>1-6</sub>-alkoxy, C<sub>2-6</sub>-alkynyl and C<sub>1-6</sub>-alkyl,
- iii) heteroaryl, and
- iv) heteroaryl substituted by 1-4 substituents individually selected from cyano,
- 15    cyano-C<sub>1-6</sub>-alkyl, halogen, halogen-C<sub>1-6</sub>-alkoxy, halogen-C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkoxy-C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkynyl-C<sub>1-6</sub>-alkoxy, C<sub>2-6</sub>-alkynyl and C<sub>1-6</sub>-alkyl;

R² is selected from the group consisting of

- i) hydrogen,
- ii) C<sub>1-6</sub>-alkyl, and
- 20    iii) halogen;

R³ is selected from the group consisting of

- i) C<sub>1-6</sub>-alkyl, and
- ii) halogen-C<sub>1-6</sub>-alkyl,

R⁴ is selected from the group consisting of

- 25    i) C<sub>1-6</sub>-alkyl,
- ii) halogen-C<sub>1-6</sub>-alkyl, and

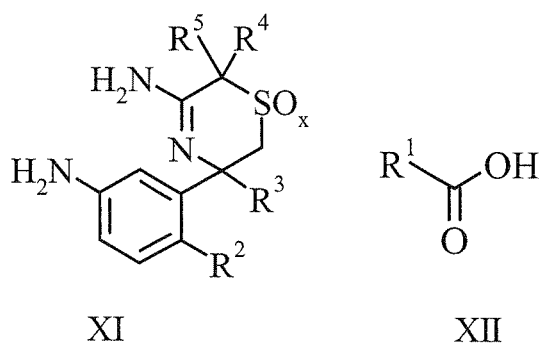
$R^5$  is selected from the group consisting of

ii) halogen-C<sub>1-6</sub>-alkyl, and

or R<sup>4</sup> and R<sup>5</sup> together form a C<sub>3-7</sub>-cycloalkyl ring, optionally substituted by one or more halogen,

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 XI to a compound of formula I.



wherein x, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> 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  $\beta$ -amyloid levels and/or  $\beta$ -amyloid oligomers and/or  $\beta$ -amyloid plaques and further deposits or 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 Alzheimer's disease.

The present compounds have Asp2 ( $\beta$ -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  $\beta$ -amyloid levels and/or  $\beta$ -amyloid oligomers and/or  $\beta$ -amyloid plaques and further deposits, particularly Alzheimer's disease.

## 5 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  $\beta$ -amyloid plaques in, on or around neurological tissue (e.g., the brain) are inhibited by the present compounds by inhibiting the A $\beta$  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 "C<sub>1-6</sub>-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 "C<sub>1-6</sub>-alkyl" are "C<sub>1-3</sub>-alkyl". Specific groups are methyl and ethyl. Most specific is methyl.

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  $\beta$ -amyloid levels and/or  $\beta$ -amyloid oligomers and/or  $\beta$ -amyloid plaques and further deposits or Alzheimer's disease.
- 5 22. A pharmaceutical composition comprising a compound of formula I according to any of claims 1-17 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.
- 10 ~~24. A method for the use in the therapeutic and/or prophylactic treatment of Alzheimer's disease, which method comprises administering a compound of formula I according to any of claims 1-17 to a human being or animal.~~

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