

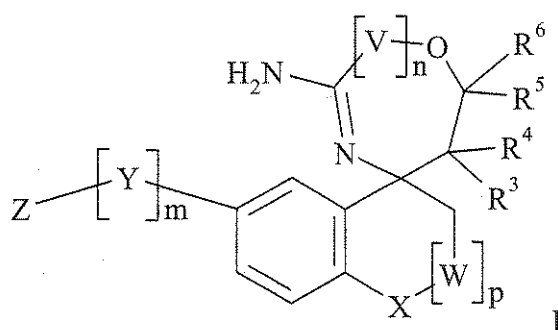
The present invention provides novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as Alzheimer's disease and type 2 diabetes. The novel compounds of formula I have improved pharmacological properties.

Field of the Invention

The present invention provides spiro-[1,3]-oxazines and spiro-[1,4]-oxazepines having BACE1 and/or BACE2 inhibitory properties, their manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

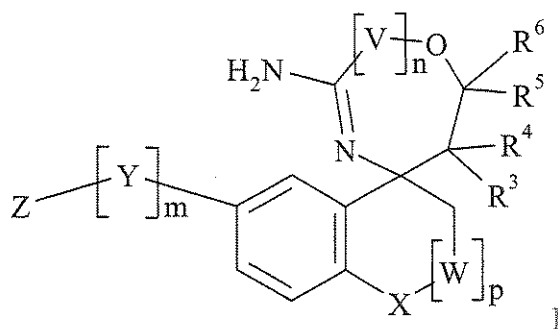
Summary of the Invention

The present invention disclosure provides a compounds of formula I,



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

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



wherein

V is $-CR^{7a}R^{7b}-$;

W is $-CR^{2a}R^{2b}-$;

X is $-CR^{1a}R^{1b}-$, $-O-$, $-S-$ or $-SO_2-$;

Y is $-NH-C=O-$;

Z is selected from the group consisting of

- i) heteroaryl,
- ii) heteroaryl substituted by 1-4 substituents individually selected from R⁸,
- iii) aryl, and
- iv) aryl substituted by 1-4 substituents individually selected from R⁸,

R^{1a} is selected from the group consisting of

- i) hydrogen,
- ii) halogen, and
- iii) C₁₋₆-alkyl;

R^{1b} is selected from the group consisting of

- i) hydrogen,
- ii) halogen, and
- iii) C₁₋₆-alkyl;

R^{2a} is selected from the group consisting of

- i) hydrogen, and
- ii) C₁₋₆-alkyl;

R^{2b} is selected from the group consisting of

- i) hydrogen,
- ii) aryl, and
- iii) C₁₋₆-alkyl;

or R^{2a} and R^{2b} together with the C they are attached form a heterocyclyl;

R³ is halogen,

R⁴ is halogen,

R⁵ is selected from the group consisting of

- i) hydrogen, and
- ii) C₁₋₆-alkyl,

R⁶ is selected from the group consisting of

- i) hydrogen, and
- ii) C₁₋₆-alkyl,

R^{7a} is selected from the group consisting of

- i) hydrogen, and
- ii) C₁₋₆-alkyl;

R^{7b} is selected from the group consisting of

- i) hydrogen, and
- ii) C₁₋₆-alkyl;

R⁸ is selected from the group consisting of

- i) cyano,
- ii) cyano-C₁₋₆-alkyl,
- iii) halogen,
- iv) halogen-C₁₋₆-alkoxy,
- v) halogen-C₁₋₆-alkyl,

vi) C₁₋₆-alkoxy,

vii) C₁₋₆-alkoxy-C₁₋₆-alkyl,

viii) C₂₋₆-alkynyl, and

ix) C₁₋₆-alkyl;

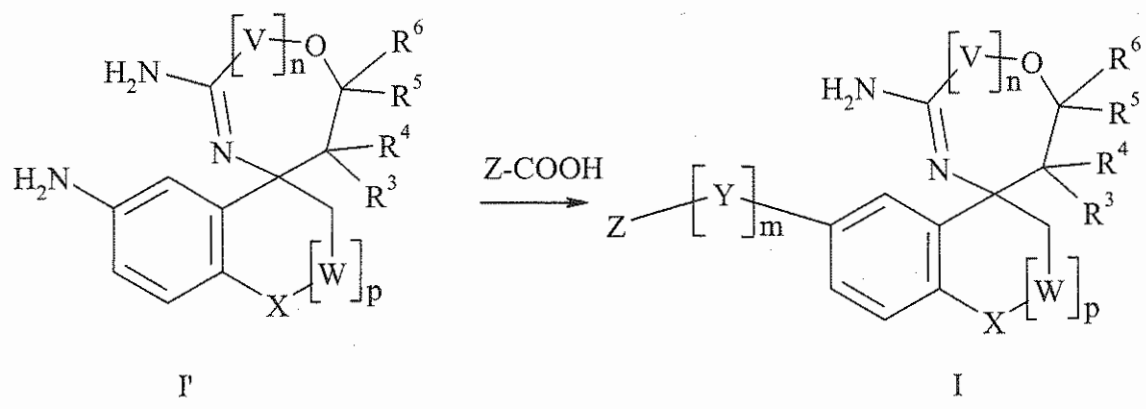
5 n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

or pharmaceutically acceptable salts thereof.

10 In a second aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises reacting a compound of formula I' to a compound of formula I



wherein V, W, Y, Z, n, p, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined above and m is 1.

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

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

20 In a fifth 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.

In a sixth 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 diabetes or type 2 diabetes.

In a seventh 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 an eighth aspect, there is provided the 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 a ninth aspect, there is provided the use of a compound of formula I as defined above for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of diabetes.

The present compounds have Asp2 (β -secretase, BACE1 or Memapsin-2) inhibitory activity and can 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. And/or the present compounds have BACE2 inhibitory activity and can therefore be used in the therapeutic and/or prophylactic treatment of diseases and disorders such as type 2 diabetes and other metabolic disorders.

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 and/or BACE2 activity, such as Alzheimer's disease and type 2 diabetes.