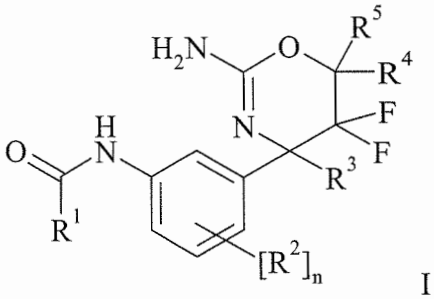
~~Difluorooxazinones as Bace 1 and/or Bace 2 inhibitors~~

Claims

1. 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}-~~lower~~ alkyl, halogen, halogen-C_{1-6}-~~lower~~ alkoxy, halogen-C_{1-6}-~~lower~~ alkyl, C_{1-6}-~~lower~~ alkoxy, C_{1-6}-~~lower~~ alkoxy-C_{1-6}-~~lower~~ alkyl and C_{1-6}-~~lower~~ alkyl,

iii) heteroaryl, and

iv) heteroaryl substituted by 1-4 substituents individually selected from amido, cyano, cyano-C_{1-6}-~~lower~~ alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkyl-C_{2-7}-~~lower~~ alkenyl, C_{3-10}-cycloalkyl-C_{2-7}-~~lower~~ alkynyl, C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~ alkyl, C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~ alkoxy, halogen, halogen-C_{1-6}-~~lower~~ alkoxy, halogen-C_{1-6}-~~lower~~ alkyl, C_{1-6}-~~lower~~ alkoxy, C_{1-6}-~~lower~~ alkoxy-C_{1-6}-~~lower~~ alkyl, C_{2-7}-~~lower~~ alkenyl, C_{2-7}-~~lower~~ alkynyl, C_{1-6}-~~lower~~ alkyl and nitro;

v) C_{1-6}-~~lower~~ alkyl,

vi) C_{1-6}-~~lower~~ alkyl substituted by 1-5 substituents individually selected from cyano, halogen, hydroxy and C_{1-6}-~~lower~~ alkoxy;

vii) C_{2-7}-~~lower~~ alkenyl,

viii) C_{2-7}-~~lower~~ alkenyl substituted by 1-4 substituents individually selected from cyano, cyano-C_{1-6}-~~lower~~ alkyl, halogen, halogen-C_{1-6}-~~lower~~ alkoxy, halogen-C_{1-6}-~~lower~~ alkyl, heteroaryl, C_{1-6}-~~lower~~ alkoxy, C_{1-6}-~~lower~~ alkoxy-C_{1-6}-~~lower~~ alkyl and C_{1-6}-~~lower~~ alkyl,

ix) C_{3-10}-cycloalkyl,

x) C_{3-10}-cycloalkyl substituted by 1-4 substituents individually selected from cyano, cyano-C_{1-6}-~~lower~~ alkyl, halogen, halogen-C_{1-6}-~~lower~~ alkoxy, halogen-C_{1-6}-~~lower~~ alkyl, C_{1-6}-~~lower~~ alkoxy, C_{1-6}-~~lower~~ alkoxy-C_{1-6}-~~lower~~ alkyl and C_{1-6}-~~lower~~ alkyl,

R^2 is selected from the group consisting of

i) hydrogen,

ii) halogen, and

iii) C_{1-6}-~~lower~~ alkyl;

R^3 is C_{1-6}-~~lower~~-alkyl;
R^4 is selected from the group consisting of
i) hydrogen, and
ii) C_{1-6}-~~lower~~-alkyl;
R^5 is selected from the group consisting of
i) hydrogen, and
ii) C_{1-6}-~~lower~~-alkyl;
n is 0, 1 or 2;
or pharmaceutically acceptable salts thereof,

wherein the term "aryl" refers to an aromatic carbocyclic group comprising 6 to 14 carbon atoms and wherein the term "heteroaryl" refers to an aromatic carbocyclic group having a single 4 to 8 membered ring or multiple condensed rings comprising 6 to 14 ring atoms and containing 1, 2 or 3 heteroatoms.

2. A compound of formula I according to claim 1, wherein

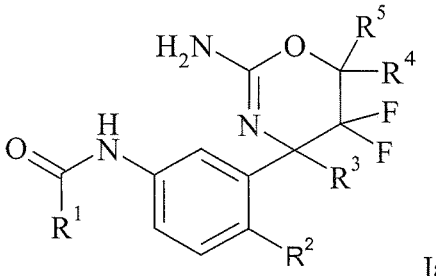
R^1 is selected from the group consisting of
i) heteroaryl, and
ii) heteroaryl substituted by 1-4 substituents individually selected from amido, cyano, cyano-C_{1-6}-~~lower~~-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkyl-C_{2-7}-~~lower~~-alkenyl, C_{3-10}-cycloalkyl-C_{2-7}-~~lower~~-alkynyl, C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~-alkyl, C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~-alkoxy, halogen, halogen-C_{1-6}-~~lower~~-alkoxy, halogen-C_{1-6}-~~lower~~-alkyl, C_{1-6}-~~lower~~-alkoxy, C_{1-6}-~~lower~~-alkoxy-C_{1-6}-~~lower~~-alkyl, C_{2-7}-~~lower~~-alkenyl, C_{2-7}-~~lower~~-alkynyl, C_{1-6}-~~lower~~-alkyl and nitro;
iii) C_{1-6}-~~lower~~-alkyl,
iv) C_{1-6}-~~lower~~-alkyl substituted by 1-5 substituents individually selected from cyano, halogen, hydroxy and C_{1-6}-~~lower~~-alkoxy;
v) C_{2-7}-~~lower~~-alkenyl,
vi) C_{2-7}-~~lower~~-alkenyl substituted by 1-4 substituents individually selected from cyano, cyano-C_{1-6}-~~lower~~-alkyl, halogen, halogen-C_{1-6}-~~lower~~-alkoxy, halogen-C_{1-6}-~~lower~~-alkyl, heteroaryl, C_{1-6}-~~lower~~-alkoxy, C_{1-6}-~~lower~~-alkoxy-C_{1-6}-~~lower~~-alkyl and C_{1-6}-~~lower~~-alkyl,
vii) C_{3-10}-cycloalkyl,
viii) C_{3-10}-cycloalkyl substituted by 1-4 substituents individually selected from cyano, cyano-C_{1-6}-~~lower~~-alkyl, halogen, halogen-C_{1-6}-~~lower~~-alkoxy, halogen-C_{1-6}-~~lower~~-alkyl, C_{1-6}-~~lower~~-alkoxy, C_{1-6}-~~lower~~-alkoxy-C_{1-6}-~~lower~~-alkyl and C_{1-6}-~~lower~~-alkyl,
R^2 is selected from the group consisting of
i) hydrogen,
ii) halogen, and
iii) C_{1-6}-~~lower~~-alkyl;
R^3 is C_{1-6}-~~lower~~-alkyl;
R^4 is selected from the group consisting of
i) hydrogen, and
ii) C_{1-6}-~~lower~~-alkyl;
R^5 is selected from the group consisting of
i) hydrogen, and

ii) C_{1-6}-~~lower~~-alkyl;

n is 0, 1 or 2;

or pharmaceutically acceptable salts thereof.

3. A compound of formula Ia according to claim 1,



Ia

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}-~~lower~~-alkyl, halogen, halogen-C_{1-6}-~~lower~~-alkoxy, halogen-C_{1-6}-~~lower~~-alkyl, C_{1-6}-~~lower~~-alkoxy, C_{1-6}-~~lower~~-alkoxy-C_{1-6}-~~lower~~-alkyl and C_{1-6}-~~lower~~-alkyl,

iii) heteroaryl, and

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

R^2 is selected from the group consisting of

i) hydrogen,

ii) halogen, and

iii) C_{1-6}-~~lower~~-alkyl;

R^3 is C_{1-6}-~~lower~~-alkyl;

R^4 is selected from the group consisting of

i) hydrogen, and

ii) C_{1-6}-~~lower~~-alkyl;

R^5 is selected from the group consisting of

i) hydrogen, and

ii) C_{1-6}-~~lower~~-alkyl;

or pharmaceutically acceptable salts thereof.

4. A compound according to any of claims 1-3, wherein R^1 is selected from the group consisting of

i) 1H-pyrazolyl, optionally substituted by 1-2 substituents individually selected from C_{3-10}-cycloalkyl, halogen, halogen-C_{1-6}-~~lower~~-alkyl, C_{1-6}-~~lower~~-alkyl,

ii) C_{3-10}-cycloalkyl, optionally substituted by 1-2 substituents individually selected from halogen and halogen-C_{1-6}-~~lower~~-alkyl,
iii) C_{2-7}-~~lower~~-alkenyl, optionally substituted by heteroaryl,
iv) C_{1-6}-~~lower~~-alkyl, optionally substituted by 1-5 substituents individually selected from halogen and hydroxy,
v) furyl, optionally substituted by nitro,
vi) isoxazolyl, optionally substituted by 1-2 C_{1-6}-~~lower~~-alkyl,
vii) oxazolyl, optionally substituted by 1-2 substituents individually selected from C_{3-10}-cycloalkyl, halogen-C_{1-6}-~~lower~~-alkyl and C_{1-6}-~~lower~~-alkyl,
viii) pyrazinyl, optionally substituted by 1-2 substituents individually selected from C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~-alkoxy, halogen, halogen-C_{1-6}-~~lower~~ alkyl and C_{1-6}-~~lower~~-alkyl,
ix) pyrazolyl, optionally substituted by 1-2 substituents individually selected from halogen and C_{1-6}-~~lower~~-alkyl,
x) pyridazinyl, optionally substituted by 1-2 halogen,
xi) pyridinyl, optionally substituted by 1-2 substituents individually selected from amido, cyano, C_{3-10}-cycloalkyl-C_{1-6}-~~lower~~-alkoxy, C_{3-10}-cycloalkyl-C_{2-7}-~~lower~~-alkynyl, halogen, halogen-C_{1-6}-~~lower~~-alkyl, C_{1-6}-~~lower~~-alkyl and halogen-C_{1-6}-~~lower~~-alkoxy; and
xii) pyrimidinyl, optionally substituted by 1-2 substituents individually selected from halogen and halogen-C_{1-6}-~~lower~~-alkyl.

5. A compound according to any of claims 1-4, wherein R^1 is selected from the group consisting of
i) pyridinyl,
ii) pyrazolyl,
iii) pyrazinyl,
iv) pyrimidinyl, and
v) pyridinyl substituted by 1-2 substituents individually selected from cyano, halogen, and halogen-C_{1-6}-~~lower~~-alkyl.

6. A compound according to any of claims 1-5, wherein R^1 is selected from the group consisting of

(2,2,2-trifluoroethoxy)-pyridin-2-yl, (cyclopropylmethoxy)pyrazin-2-yl, (trifluoromethyl) pyrazin-2-yl, 1-(difluoromethyl)-1H-pyrazol-3-yl, 1-(trifluoromethyl)cycloprop-1-yl, 1-furyl-ethenyl, 1-methyl-1H-pyrazol-3-yl, 2-(chloromethyl)oxazol-4-yl, 2-(fluoromethyl)oxazol-4-yl, 2,2,2-trifluoro-1-hydroxy-1-methyl-2-ethyl, 2,2-difluorocycloprop-1-yl, 2,5-dimethyloxazol-4-yl, 2-ethyloxazol-4-yl, 2-methyl-5-(trifluoromethyl)oxazol-4-yl, 2-methyloxazol-4-yl, 3-(2,2,2-trifluoroethoxy)-pyridin-2-yl, 3,5-dichloropyrazin-2-yl, 3,5-dichloro-pyridin-2-yl, 3,5-difluoro-pyridin-2-yl, 3-chloro-5-cyano-pyridin-2-yl, 3-chloro-5-fluoro-pyridin-2-yl, 3-chloro-5-trifluoromethyl-pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-fluoro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 4-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl, 4-chloro-1-(2,2-difluoroethyl)-

25. A compound of formula I according to claims 1 to 18 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, macrophagic myofasciitis, juvenile idiopathic arthritis, granulomatous arthritis, malignant melanoma, multiple mieloma, rheumatoid arthritis, Sjogren syndrome, SpinoCerebellar Ataxia 1, SpinoCerebellar Ataxia 7, Whipple's Disease or Wilson's Disease.

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

~~27. Use of a compound of formula I according to any of claims 1 to 18 for the manufacture of a medicament for the use in inhibition of BACE1 and/or BACE2 activity.~~

~~28. Use of a compound of formula I according to any of claims 1 to 18 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.~~

~~29.~~ 27. Use of a compound of formula I according to any of claims 1 to 18 for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of diabetes, particularly type 2 diabetes.

~~30. A compound of formula I according to any of claims 1 to 18 for the use in inhibition of BACE1 and/or BACE2 activity.~~

~~31. A compound of formula I according to claims 1 to 18 for the use 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.~~

28. A compound of formula I according to claims 1 to 18 for the use in the therapeutic and/or prophylactic treatment of diabetes, particularly type 2 diabetes.

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