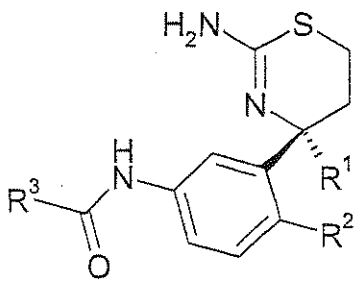
is stored in secretory granules of mouse and rat pancreatic beta cells", Ultrastruct Pathol. 2008, 32(6), 246-251). It is also known to be capable of degrading APP (I Hussain, D Powell, D Howlett, G Chapman et al., "ASP1 (BACE2) cleaves the amyloid precursor protein at the β-secretase site" Mol Cell Neurosci. 2000, 16, 609-619), IL-1R2 (P Kuhn, E Marjaux, A Imhof, B De Strooper et al., "Regulated intramembrane proteolysis of the interleukin-1 receptor II by alpha-, beta-, and gamma-secretase" J. Biol. Chem. 2007, 282(16), 11982-11995).

Inhibition of BACE2 is therefore proposed as a treatment for type 2 diabetes with the potential to preserve and restore beta-cell mass and stimulate insulin secretion in pre-diabetic and diabetic patients. It is therefore an object of the embodiments disclosed herein~~present invention~~ to provide selective BACE2 inhibitors. Such compounds are useful as therapeutically active substances, particularly in the treatment and/or prevention of diseases which are associated with the inhibition of BACE2.

In a first aspect, there is provided the use of a compound of the formula



I

wherein

R^1 is C_{1-7}-alkyl or C_{3-7}-cycloalkyl;

R^2 is selected from the group consisting of hydrogen, C_{1-7}-alkyl, halogen, cyano and C_{1-7}-alkoxy;

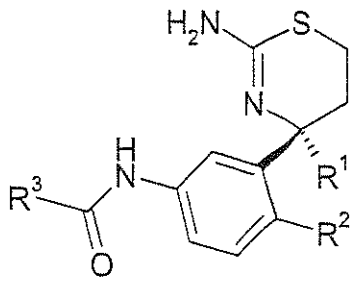
R^3 is aryl or heteroaryl, said aryl or heteroaryl being unsubstituted or substituted by one, two or three groups selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy, cyano, hydroxy-C_{1-7}-alkyl, oxo and phenyl;

or pharmaceutically acceptable salts thereof,

for the preparation of a medicament for the treatment or prevention of diabetes,

wherein the term "heteroaryl" refers to an aromatic or partly unsaturated 5- or 6-membered ring which comprises at least one heteroatom selected from nitrogen, oxygen and/or sulphur; or to bicyclic aromatic or partly unsaturated groups comprising two 5- or 6-membered rings, in which one or both rings can contain one, two or three atoms selected from nitrogen, oxygen or sulphur, said heteroaryl being selected from the group consisting of pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 6-oxo-1,6-dihydropyridazinyl, 5-oxo-4,5-dihydropyrazinyl, pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, thieno[2,3-c]pyridyl, quinoxalinyl, benzo[b]thienyl, benzothiazolyl, benzotriazolyl, indolyl, indazolyl and 3,4-dihydro-1H-isoquinolinyl.

In a second aspect, there is provided a compound of the formula I having the formula



Ia

wherein

R^1 is ethyl;

R^2 is selected from the group consisting of C_{1-7}-alkyl, halogen, cyano and C_{1-7}-alkoxy;

R^3 is aryl or heteroaryl, said aryl or heteroaryl being unsubstituted or substituted by one, two or three groups selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy, cyano, hydroxy-C_{1-7}-alkyl, oxo and phenyl;

or pharmaceutically acceptable salts thereof,

wherein the term "heteroaryl" refers to an aromatic or partly unsaturated 5- or 6-membered ring which comprises at least one heteroatom selected from nitrogen, oxygen and/or sulphur; or to bicyclic aromatic or partly unsaturated groups comprising two 5- or 6-membered rings, in which one or both rings can contain one, two or three atoms selected from nitrogen, oxygen or sulphur, said heteroaryl being selected from the group consisting of pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 6-oxo-1,6-dihydropyridazinyl, 5-oxo-4,5-dihydropyrazinyl, pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, thieno[2,3-c]pyridyl, quinoxalinyl, benzo[b]thienyl, benzothiazolyl, benzotriazolyl, indolyl, indazolyl and 3,4-dihydro-1H-isoquinolinyl.

In a third aspect, there is provided a pharmaceutical composition comprising a compound of formula Ia as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The compounds of the present disclosure~~invention~~ exceed the compounds known in the art, inasmuch as they are strong and selective inhibitors of BACE2. They are expected to have an enhanced therapeutic potential compared to the compounds already known in the art and can be used for the treatment and prevention of diabetes, preferably type 2 diabetes, metabolic syndrome and a wide range of metabolic disorders.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred, and with fluorine and chlorine being more preferred.

The term "lower alkyl" or "C_{1-7}-alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 7 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched C_{1-7} alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls and the isomeric heptyls, preferably methyl and ethyl and most preferred methyl.

The term "lower alkoxy" or "C_{1-7}-alkoxy" refers to the group R'-O-, wherein R' is lower alkyl and the term "lower alkyl" has the previously given significance. Examples of lower alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy, preferably methoxy and ethoxy.

The term "lower halogenalkyl" or "halogen-C_{1-7}-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred lower