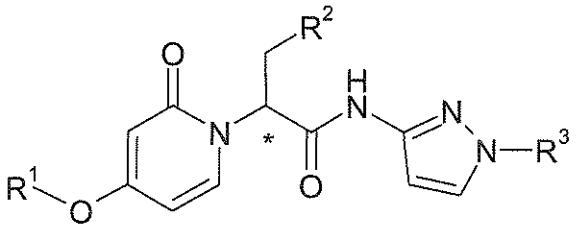
10, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β-cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* **309**, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. et al., *New England J. Med.* **338**, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in β-cells and hepatocytes, which will be coupled to increased insulin secretion. Such agents would be useful for treating type II diabetes.

~~In an embodiment of~~ the present disclosure~~invention,~~ provide~~d~~s ~~is~~for a compound of formula (I):



(I),

wherein

R^1 is aryl, said aryl being unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl, lower halogenalkyl, lower alkoxy or lower halogenalkoxy, or

heteroaryl, said heteroaryl being unsubstituted or substituted with halogen or lower alkyl, or

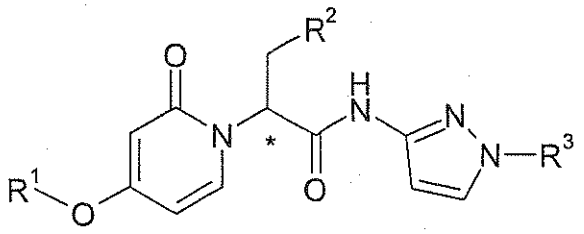
R^2 is selected from the group consisting of lower alkyl, lower halogenalkyl, and cycloalkyl, said cycloalkyl being unsubstituted or substituted by halogen, oxo or hydroxy; and

R^3 is lower alkyl or lower halogenalkyl;

or pharmaceutically acceptable salts thereof.

* denotes an asymmetric C-atom.

In a first aspect, provided is a compound of formula (I)



(I),

wherein

R^1 is aryl, said aryl being unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 halogenalkyl, C_1-C_6 alkoxy or C_1-C_6 halogenalkoxy, or

heteroaryl, said heteroaryl being unsubstituted or substituted with halogen or C_1-C_6 alkyl, or

R^2 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 halogenalkyl, and cycloalkyl, said cycloalkyl being unsubstituted or substituted by halogen, oxo or hydroxy; and

R^3 is C_1-C_6 alkyl or C_1-C_6 halogenalkyl;

or pharmaceutically acceptable salts thereof.

In a second aspect~~still yet another preferred embodiment of the present invention~~, provided is a pharmaceutical composition, comprising a therapeutically effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and/or adjuvant.

In a preferred embodiment, R^1 is aryl, said aryl being unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl, lower halogenalkyl, lower alkoxy or lower halogenalkoxy. In another preferred embodiment, R^1 is aryl, said aryl being unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl or alkoxy.

In a further preferred embodiment, R^1 is aryl selected from phenyl or naphthalen-1-yl.

In another preferred embodiment, R^1 is phenyl, unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl, lower halogenalkyl, lower alkoxy or lower halogenalkoxy. In another preferred embodiment, R^1 is phenyl, unsubstituted or mono-, bi- or tri-substituted with fluorine, chlorine, phenyl, $-CF_3$, $-CH_3$, $-OCF_3$, $-OCH_3$ or $-CH(CH_3)_2$.

In another preferred embodiment, R^1 is phenyl bi-substituted with fluorine.

In another preferred embodiment, R^1 is phenyl substituted with both chlorine and $-CH_3$.

In another preferred embodiment, R^1 is naphthalen-1-yl.

In another preferred embodiment, R^1 is heteroaryl, unsubstituted or substituted with halogen or lower alkyl. In another preferred embodiment, R^1 is pyridyl, unsubstituted or substituted with halogen or lower alkyl.

In another preferred embodiment, R^1 is unsubstituted pyridine.

In another preferred embodiment, R^2 is $-CH(CH_3)_2$.

In another preferred embodiment, R^3 is lower alkyl, more preferably methyl.

In a further embodiment of the present ~~invention~~disclosure, provided is a compound of formula (I), wherein

R^1 is -aryl, unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl or alkoxy,

4-methyl-2-[4-(naphthalen-1-yloxy)-2-oxo-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-chloro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-[2-oxo-4-(2-trifluoromethoxy-phenoxy)-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-fluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide; or
2-[4-(2-methoxy-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide.

In a still yet another preferred embodiment of the present ~~invention~~disclosure, provided are pharmaceutical compositions, comprising a therapeutically effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In a third aspect, provided is a compound of formula (I) as defined above for use as therapeutic active substance.

In a fourth aspect, provided is a compound of formula (I) as defined above for use in the treatment of a metabolic disease and/or disorder.

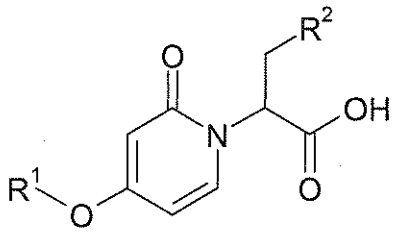
In a further embodiment, the ~~invention~~disclosure is concerned with a compound of formula (I) for use as therapeutic active substance, preferably for use in treating a metabolic disease and/or disorder, more preferably, for use in the treatment of diabetes mellitus.

In another preferred embodiment, the ~~invention~~disclosure relates to the use of a compound of formula (I) for the preparation of a medicament for treating a metabolic disease and/or disorder, preferably for the preparation of a medicament for the treatment of diabetes mellitus.

In still another embodiment, provided is a method for treating a metabolic disease and/or disorder, comprising the step of administering a therapeutically effective amount of a compound of formula (I) to a patient in need thereof.

In a further embodiment, the ~~invention~~disclosure relates to a process for the preparation of compounds of formula I, which process comprises

reacting a compound of the formula (IX)

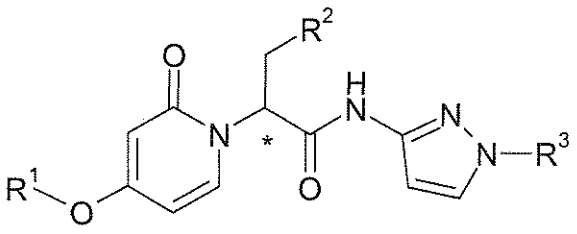


(IX)

wherein R^1 and R^2 are as defined in claim 1,
with a compound of the formula (XI)

Claims

1. A compound of formula (I)



(I),

wherein

R^1 is aryl, said aryl being unsubstituted or mono-, bi- or tri-substituted independently with halogen, phenyl, ~~lower~~ C_1-C_6 alkyl, C_1-C_6 ~~lower~~ halogenalkyl, C_1-C_6~~lower~~ alkoxy or C_1-C_6 ~~lower~~ halogenalkoxy, or

heteroaryl, said heteroaryl being unsubstituted or substituted with halogen or C_1-C_6 ~~lower~~ alkyl, or

R^2 is selected from the group consisting of C_1-C_6 ~~lower~~ alkyl, C_1-C_6 ~~lower~~ halogenalkyl, and cycloalkyl, said cycloalkyl being unsubstituted or substituted by halogen, oxo or hydroxy; and

R^3 is C_1-C_6 ~~lower~~ alkyl or C_1-C_6 ~~lower~~ halogenalkyl;

or pharmaceutically acceptable salts thereof.

~~2. The compound according to claim 1, wherein R^1 is aryl, unsubstituted or mono-, bi- or tri-substituted independently with mono-, bi- or tri-substituted independently with halogen, phenyl, lower alkyl, lower halogenalkyl, lower alkoxy or lower halogenalkoxy.~~

~~3~~2. The compound according to claims 1 ~~or 2~~, wherein R^1 is phenyl, unsubstituted or mono-, bi- or tri-substituted independently with mono-, bi- or tri-substituted independently with halogen, phenyl, C_1-C_6 ~~lower~~ alkyl, C_1-C_6 ~~lower~~ halogenalkyl, C_1-C_6 ~~lower~~ alkoxy or C_1-C_6 ~~lower~~ halogenalkoxy.

~~4~~3. The compound according to ~~any one of~~ claims 1 ~~to 3~~or 2, wherein R^1 is phenyl, unsubstituted or substituted with fluorine, chlorine, phenyl, $-CF_3$, $-CH_3$, $-OCF_3$, $-OCH_3$ or $-CH(CH_3)_2$.

~~5~~4. The compound according to any one of claims 1 to 3, wherein R^1 is phenyl bi-substituted with fluorine or phenyl substituted with both chlorine and $-CH_3$.

~~6. The compound according to claim 1, wherein R^1 is heteroaryl, unsubstituted or substituted with halogen or lower alkyl.~~

~~7~~5. The compound according to claims 1 or ~~6~~4, wherein R^1 is pyridine, unsubstituted or substituted with halogen or C_1-C_6 ~~lower~~ alkyl.

~~8~~6. The compound according to claim 1, wherein R^1 is naphthalen-1-yl.

~~9~~7. The compound according to any one of claims 1 to ~~8~~6, wherein R^2 is C_1-C_6 ~~lower~~ alkyl.

~~10~~8. The compound according to any one of claims 1 to ~~9~~7, wherein R^2 is $-CH(CH_3)_2$.

~~11~~9. The compound according to any one of claims 1 to ~~10~~8, wherein R^3 is C_1-C_6 ~~lower~~ alkyl.

~~12~~10. The compound according to any one of claims 1 to ~~11~~9, wherein R^3 is methyl.

~~13~~11. The compound according to claim 1, wherein said compound is selected from the group consisting of
2-[4-(2,3-difluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(3-fluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-(2-oxo-4-phenoxy-2H-pyridin-1-yl)-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-(2-oxo-4-o-tolyloxy-2H-pyridin-1-yl)-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2,6-difluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-[2-oxo-4-(2-trifluoromethyl-phenoxy)-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(4-fluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-[2-oxo-4-(pyridin-3-yloxy)-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(biphenyl-2-yloxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-isopropyl-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;

2-[4-(2,4-difluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(3-chloro-2-methyl-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2,5-difluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-[4-(naphthalen-1-yloxy)-2-oxo-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-chloro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
4-methyl-2-[2-oxo-4-(2-trifluoromethoxy-phenoxy)-2H-pyridin-1-yl]-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-fluoro-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide;
2-[4-(2-methoxy-phenoxy)-2-oxo-2H-pyridin-1-yl]-4-methyl-pentanoic acid (1-methyl-1H-pyrazol-3-yl)-amide,
or a pharmaceutically acceptable salt thereof.

~~14~~12. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to ~~13~~ 11 and a pharmaceutically acceptable carrier and/or adjuvant.

~~15~~13. The compound of formula (I) according to any one of claims 1 to ~~13~~ 11 for use as therapeutic active substance.

~~16~~14. The compound of formula (I) according to any one of claims 1 to ~~13~~ 11 for use in the treatment of a metabolic disease and/or disorder.

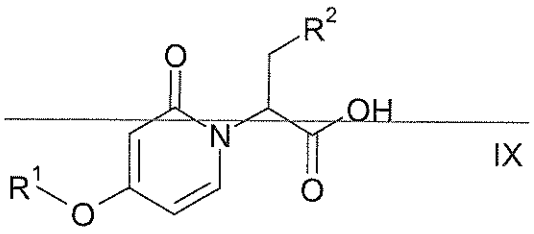
~~17~~15. The compound of formula (I) according to claim ~~16~~ 14 for use in the treatment of diabetes mellitus.

~~18. The use of a compound of formula (I) according to any one of claims 1 to 13 for the preparation of a medicament for the treatment of diabetes mellitus.~~

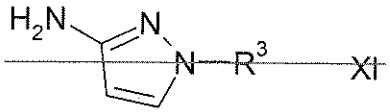
~~19. A method for treating a metabolic disease and/or disorder, comprising the step of administering a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 13 to a patient in need thereof.~~

~~20. A process for the preparation of a compound of formula (I) according to any one of claims 1 to 13, which process comprises~~

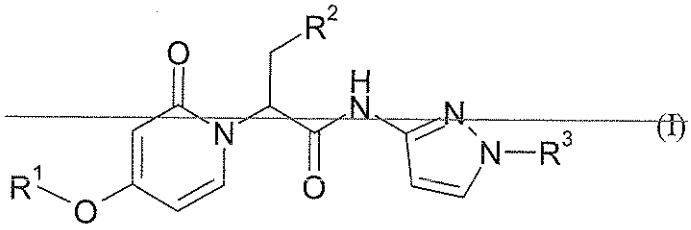
reacting a compound of the formula (IX)



wherein R^1 and R^2 are as defined in claim 1,
with a compound of the formula (XI)



wherein R^3 is as defined in claim 1, in the presence of an amide coupling reagent and a base to obtain a compound of the formula (I)



and, if desired, converting the compound of formula (I) into a pharmaceutically acceptable salt.