

GIP on the insulin release, and the other release incretins may also contribute to an overall beneficial contribution of GPR40 modulation on metabolic diseases. The indirect contributions of GPR40 modulation on insulin release through the elevation of plasma levels of incretins may be further augmented by the coadministration of inhibitors of the enzymes responsible for the incretin degradation, such as inhibitors of DPP-4.

Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease. The modulation of the function of GPR40 in modulating insulin secretion indicates the therapeutic agents capable of modulating GPR40 function could be useful for the treatment of disorders such as diabetes and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

Object of the present invention

The object of the embodiments disclosed herein ~~present invention~~ is to provide new compounds, hereinafter described as compounds of formula (I), in particular new 2,3-indanyloxydihydrobenzofuranylacetic acids, which are active with regard to the G-protein-coupled receptor GPR40, notably are agonists of the G-protein-coupled receptor GPR40.

A further object of the the embodiments disclosed herein ~~present invention~~ is to provide new compounds, in particular new indanyloxydihydrobenzofuranylacetic acids, which have an activating effect on the G-protein-coupled receptor GPR40 *in vitro* and/or *in vivo* and possess suitable pharmacological and pharmacokinetic properties to use them as medicaments.

A further object of the the embodiments disclosed herein ~~present invention~~ is to provide effective GPR40 agonists, in particular for the treatment of metabolic disorders, for example diabetes, dyslipidemia and/or obesity.

A further object of the the embodiments disclosed herein ~~present invention~~ is to provide methods for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 in a patient.

A further object of the ~~the embodiments disclosed herein~~ ~~present invention~~ is to provide a pharmaceutical composition comprising at least one compound according to the invention.

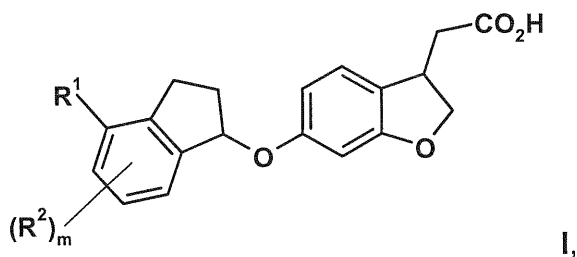
A further object of the ~~the embodiments disclosed herein~~ ~~present invention~~ is to provide a combination of at least one compound according to the invention with one or more additional therapeutic agents.

Further objects of the ~~the embodiments disclosed herein~~ ~~present invention~~ become apparent to the one skilled in the art by the description hereinbefore and in the following and by the examples.

GPR40 modulators are known in the art, for example, the compounds disclosed in WO 2004041266 (EP 1559422), WO 2007033002 and WO 2009157418. The indanyloxydihydrobenzofuranylacetic acids of the present invention may provide several advantages, such as enhanced potency, high metabolic and/or chemical stability, high selectivity and tolerability, enhanced solubility, and the possibility to form stable salts.

Summary of the ~~Invention~~ Disclosure

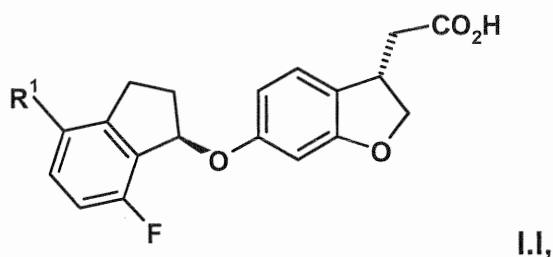
In a first aspect the ~~invention~~ disclosure relates to a compound of formula I



wherein

R^1 is selected from the group R^1 -G1 consisting of a phenyl ring, a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-;

wherein optionally a second ring is annulated to said phenyl or heteroaromatic ring, wherein said second ring is 5- or 6-membered, partially unsaturated or aromatic and may contain 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that only up to two of the



wherein R¹ is defined as mentioned hereinbefore under formula I,

- 5 the isoforms, tautomers, stereoisomers, metabolites, prodrugs, solvates, hydrates, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

10 The expression "optionally substituted with 1 or more F atoms" means that none or one up to successively all H atoms bound to carbon atoms of the respective group or submoiety may be replaced by F atoms, preferably 1 to 5 H atoms or, more preferred, 1 to 3 H atoms may be replaced by F atoms.

15 The extension -G_n used within the definitions is meant to identify genus n of the respective substituent. For example, R¹-G₁ defines genus 1 of the substituent R¹.

In a further aspect, this disclosure relates to a pharmaceutically acceptable salt of a compound of general formula I or I.I.

20 In a further aspect this ~~invention~~ disclosure relates to a pharmaceutical composition, comprising one or more compounds of general formula I or I.I, or one or more pharmaceutically acceptable salts thereof according to the invention, optionally together with one or more inert carriers and/or diluents.

25 In a ~~further aspect~~ an embodiment, this ~~disclosure~~ invention relates to a method for treating diseases or conditions which are mediated by activating the G-protein-coupled receptor GPR40 in a patient in need thereof characterized in that a compound of general formula I or I.I, or a pharmaceutically acceptable salt thereof is administered to the patient.

According to an embodiment ~~another aspect of the disclosure~~invention, there is provided a method for treating a metabolic disease or disorder, such as diabetes, dyslipidemia and/or obesity, in a patient in need thereof characterized in that a therapeutically effective amount of a

compound of general formula I or I.I, or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the disclosure, there is provided use of a compound of the general formula I or I.I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

According to another aspect an embodiment of the disclosure invention, there is provided the use of a compound of the general formula I or I.I, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for a therapeutic method as described hereinbefore and hereinafter.

According to another aspect of the disclosure, there is provided a compound of the general formula I or I.I or a pharmaceutically acceptable salt thereof for use as a medicament.

According to another aspect of the disclosure, there is provided a compound of the general formula I or I.I or a pharmaceutically acceptable salt thereof for use in the treatment of diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for use in the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

According to another aspect of the disclosure invention, there is provided a compound of the general formula I or I.I, or a pharmaceutically acceptable salt thereof for use in a therapeutic method as described hereinbefore and hereinafter.

In an embodiment, a further aspect this disclosure invention relates to a method for treating a disease or condition mediated by the activation of the G-protein-coupled

receptor GPR40 in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of a compound of the general formula I or I.I, or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of one or more additional therapeutic agents.

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In an embodiment, ~~a further aspect this disclosure invention~~ relates to the use of a compound of the general formula I or I.I, or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents for the treatment of diseases or conditions which are mediated by the activation of the G-protein-coupled receptor GPR40.

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In a further aspect this disclosure invention relates to a pharmaceutical composition which comprises a compound according to general formula I or I.I, or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

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Other aspects of the disclosure invention become apparent to the one skilled in the art from the specification and the experimental part as described hereinbefore and hereinafter.

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Detailed Description

C₃-alkyl-S(=O)₂- substituted with 1 HO- or H₃C-O- group;

and

phenyl, furanyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyridin-2-onyl, pyrimidin-2-onyl, pyrimidin-4-onyl and pyridazin-3-onyl, wherein a NH group, if present, optionally is replaced by N-CH₃, N-CH₂-C(CH₃)₂-OH or N-C(CH₃)₂-CH₂-OH, and which are optionally substituted with 1 H₃C- group and optionally substituted with 1 group selected from -CH₃, -CH₂-CH₃, cyclopropyl, -C(CH₃)₂-OH, and -O-CH₃;

or a salt thereof.

9. A pharmaceutically acceptable salt of a compound according to one or more of the claims 1 to 8.

10. A pharmaceutical composition comprising one or more compounds according to one or more of the claims 1 to 8 or one or more pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

11. Use of a compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of A method for treating diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia in a patient in need thereof, characterized in that a compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof is administered to the patient.

12. A compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof for use as a medicament.

13. A compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof for use in the treatment of diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for use in the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with