SUMMARY ~~OF THE INVENTION~~

Applicants have unexpectedly found that GPR41 is expressed in pancreatic islet cell lines and GPR41 is upregulated in db/db diabetic mice. In addition, Applicants have identified agonist compounds that modulate GPR41 function and have found that these compounds decrease insulin secretion. Further, Applicants disclose inverse agonists or antagonists of GPR41 that can be used to increase insulin secretion for the treatment of insulin-related disorders such as insulin resistance, impaired glucose tolerance and diabetes.

In one aspect, there is provided an in vitro method for identifying a glycemic stabilizing compound, comprising: a) contacting a candidate compound with GPR41, and b) determining whether GPR41 functionality is modulated, wherein a modulation in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound; said GPR41 having an amino acid sequence as shown in SEQ ID NO:2, or a variant or ortholog thereof, wherein said variant is an allelic variant, splice variant or conservative amino acid substitution variant of GPR41.

In a ***first*** embodiment~~aspect~~, the disclosure~~invention~~ features a method for identifying a glycemic stabilizing compound, comprising: a) contacting a candidate compound with GPR41, and b) determining whether GPR41 functionality is modulated, wherein a modulation in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound. In some embodiments, said GPR41 is human. In some embodiments, said determining comprises a second messenger assay. In some embodiments, a glycemic stabilizing compound comprises a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided glycemic stabilizing compound identified by the method as defined herein selected from the following compounds and pharmaceutically acceptable salts thereof:

2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide,

4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide,

2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-((5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydroquinoline=3-carboxylic acid (2-chloro-phenyl)-amide,

2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and

4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide.

In a ***second*** embodimentaspect, the disclosureinvention features a glycemic stabilizing compound identified according to a method of the first embodimentaspect. In some embodiments, said glycemic stabilizing compound is a GPR41 agonist, for example, a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxyiic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof. In some embodiments, said glycemic stabilizing compound is a GPR41 inverse agonist or antagonist, for example, a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a method for preparing a composition comprising a glycemic stabilizing compound said method including admixing said compound with a carrier, wherein said compound is a compound as defined herein.

In a ***third*** embodimentaspect, the disclosureinvention features a method for preparing a composition which comprises identifying a glycemic stabilizing compound and then admixing said compound with a carrier, wherein said compound is identified by a method of the first embodimentaspect.

In one aspect, there is provided a pharmaceutical composition comprising, consisting essentially of, or consisting of a compound as defined herein.

In a ***fourth*** embodimentaspect, the disclosureinvention features a pharmaceutical composition comprising, consisting essentially of, or consisting of a compound of the second embodimentaspect.

In one aspect, there is provided a compound as defined herein for use in a method of treatment of human or animal body by therapy.

In one aspect, there is provided a compound as defined herein for use in a method of treatment of an insulin-related disorder.

In one aspect, there is provided the use of a compound as defined herein in the manufacture of a medicament for the treatment of an insulin-related disorder.

In one aspect, there is provided a compound as defined herein for use in a method of treatment of hypoglycemia, an insulin-secreting or insulin-dependent tumor, insulin resistance, impaired glucose tolerance, or diabetes.

In one aspect, there is provided the use of a compound as defined herein in the manufacture of a medicament for the treatment of hypoglycemia, an insulin-secreting or insulin-dependent tumor, insulin resistance, impaired glucose tolerance, or diabetes.

In one aspect, there is provided a compound as defined herein for use in a method of treatment of the human body by therapy.

In a ***fifth*** embodiment~~aspect~~, the disclosure~~invention~~ features a method for treating or preventing an insulin-related disorder in an individual in need thereof, comprising administering to said individual an effective amount of a compound of the fourth embodiment~~aspect~~. In some

embodiments, said insulin-related disorder is hypoglycemia, an insulin-secreting or insulin-dependent tumor, aging, insulin resistance, impaired glucose tolerance, or diabetes. In some embodiments, a method of the fifth embodimentaspect further comprises administering to said individual an effective amount of an agent used for the treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of a compound of the fourth embodimentaspect. In some embodiments, the individual is a mammal and in some embodiments the individual is a human.

In a ***sixth*** embodimentaspect, the disclosureinvention features a method for the manufacture of a medicament comprising a compound of the fourth embodimentaspect for use as a glycemic stabilizing compound and a method for the manufacture of a medicament comprising a compound of the fourth embodimentaspect for use in the treatment of an insulin-related disorder.

In a ***seventh*** embodimentaspect, the disclosureinvention features a method for identifying a glycemic stabilizing compound, comprising: a) contacting a candidate compound with GPR41, and b) determining whether GPR41 functionality is increased, wherein an increase in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound. In some embodiments, said GPR41 is human. In some embodiments, said determining comprises a second messenger assay. In some embodiments, a glycemic stabilizing compound comprises a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

In an ***eighth*** embodimentaspect, the disclosureinvention features a glycemic stabilizing compound identified according to a method of the seventh embodimentaspect. In some embodiments, said glycemic stabilizing compound is a GPR41 agonist, for example, a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-

[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

In a ***ninth*** embodimentaspect, the disclosureinvention features a method for preparing a composition which comprises identifying a glycemic stabilizing compound and then admixing said compound with a carrier, wherein said compound is identified by a method of the seventh embodimentaspect.

In a ***tenth*** embodimentaspect, the disclosureinvention features a pharmaceutical composition comprising, consisting essentially of, or consisting of a compound of the eighth embodimentaspect.

In a ***eleventh*** embodimentaspect, the disclosureinvention features a method for treating or preventing an insulin-related disorder in an individual in need thereof, comprising administering to said individual an effective amount of a compound of the tenth embodimentaspect. In some embodiments, said insulin-related disorder is hypoglycemia, an insulin-secreting or insulin-dependent tumor, or aging. In some embodiments, the individual is a mammal and in some embodiments the individual is a human.

In a ***twelfth*** embodimentaspect, the disclosureinvention features a method for the manufacture of medicament comprising a compound of the eighth embodimentaspect for use as a glycemic stabilizing compound and a method for the manufacture of a medicament comprising a compound of the eighth embodimentaspect for use in the treatment of an insulin-related disorder.

In a ***thirteenth*** embodimentaspect, the disclosureinvention features a method for identifying a glycemic stabilizing compound, comprising: a) contacting a candidate compound with GPR41, and b) determining whether GPR41 functionality is decreased, wherein a decrease in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound. In some embodiments, said GPR41 is human. In some embodiments, said determining comprises a second messenger assay. In some embodiments, said glycemic stabilizing compound comprises a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-

oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In a ***fourteenth*** embodimentaspect, the disclosureinvention features a glycemic stabilizing compound identified according to a method of the thirteenth embodimentaspect. In some embodiments, said glycemic stabilizing compound is a GPR41 inverse agonist or antagonist. In some embodiments, said glycemic stabilizing compound comprises a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In a ***fifteenth*** embodimentaspect, the disclosureinvention features a method for preparing a composition which comprises identifying a glycemic stabilizing compound and then admixing said compound with a carrier, wherein said compound is identified by a method of the thirteenth embodimentaspect.

In a ***sixteenth*** embodimentaspect, the disclosureinvention features a pharmaceutical composition comprising, consisting essentially of, or consisting of a compound of the fourteenth embodimentaspect.

In a ***seventeenth*** embodimentaspect, the disclosureinvention features a method for treating or preventing an insulin-related disorder in an individual in need thereof, comprising administering to said individual an effective amount of a compound of the sixteenth embodimentaspect. In some embodiments, said insulin-related disorder is insulin resistance, impaired glucose tolerance, or diabetes. In some embodiments, a method of the seventeenth embodimentaspect further comprises administering to said individual an effective amount of an agent used for the

treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of a compound of the sixteenth embodimentaspect. In some embodiments, the individual is a mammal and in some embodiments the individual is a human.

In a ***eighteenth*** embodimentaspect, the disclosureinvention features a method for the manufacture of a medicament comprising a compound of the sixteenth embodimentaspect for use as a glycemic stabilizing compound and a method for the manufacture of a medicament comprising a compound of the sixteenth embodimentaspect for use in the treatment of an insulin-related disorder.

In a ***nineteenth*** embodimentaspect, the disclosureinvention features a method for increasing GPR41 function comprising contacting GPR41 with an effective amount of a GPR41 agonist. In some embodiments, said agonist comprises a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

In a ***twentieth*** embodimentaspect, the disclosureinvention features a method for decreasing GPR41 function comprising contacting GPR41 with an effective amount of a GPR41 inverse agonist or antagonist. In some embodiments, said inverse agonist or antagonist comprises a compound selected from the group consisting of, 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In a *twenty first* embodimentaspeet, the disclosureinvention features a method for treating or preventing an insulin-related disorder, comprising administering to an individual in need thereof an effective amount of a GPR41 modulator. In some embodiments, said insulin-related disorder is hypoglycemia, an insulin-secreting or insulin-dependent tumor, or aging and said modulator is an agonist, for example, a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof. In some embodiments, said insulin-related disorder is insulin resistance, impaired glucose tolerance, or diabetes and said modulator is an inverse agonist or antagonist, for example, a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof. In some embodiments, a method of the twenty first embodimentaspeet further comprises administering to said individual an effective amount of an agent used for the treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of a GPR41 inverse agonist or antagonist.

In a ***twenty second*** embodimentaspeet, the disclosureinvention features a method for treating or preventing a disorder treatable or preventable by increasing GPR41 function, comprising administering to an individual in need thereof an effective amount of a compound

selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof. In some embodiments, said disorder is an insulin-related disorder, for example, hypoglycemia, an insulin-secreting or insulin-dependent tumor, or aging.

In a ***twenty third*** embodimentaspect, the disclosureinvention features a method for treating or preventing a disorder treatable or preventable by decreasing GPR41 function, comprising administering to an individual in need thereof an effective amount of a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof. In some embodiments, said disorder is an insulin-related disorder, for example, insulin resistance, impaired glucose tolerance, or diabetes. In some embodiments, said insulin-related disorder is Type II diabetes. In some embodiments, a method of the twenty third embodimentaspect further comprises administering to said individual an effective amount of an agent used for the treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of a GPR41 inverse agonist or antagonist.

In a ***twenty fourth*** embodimentaspect, the disclosureinvention features a method for increasing blood glucose levels in an individual in need thereof, comprising administering to the

individual an effective amount of a GPR41 agonist, for example, a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

In a ***twenty fifth*** embodiment~~aspect~~, the disclosure~~invention~~ features a method for decreasing blood glucose levels in an individual in need thereof, comprising administering to the individual an effective amount of a GPR41 inverse agonist or antagonist, for example, a compound selected from the group consisting of: 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

In a ***twenty sixth*** embodiment~~aspect~~, the disclosure~~invention~~ features a method for decreasing insulin secretion in an individual in need thereof, comprising administering to the individual an effective amount of a GPR41 agonist, for example, a compound selected from the group consisting of: 2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-

tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

In a ***twenty seventh*** embodiment~~aspect~~, the disclosure~~invention~~ features a method for increasing insulin secretion in an individual in need thereof, comprising administering to the individual an effective amount of a GPR41 inverse agonist or antagonist, for example, a compound selected from the group consisting of2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows dot blot analysis of human GPR41 expression in human adult and fetal tissues.

Figure 2 shows RT-PCR and TaqMan quantitative PCR analysis of mouse GPR41 expression in selected tissues of normal and mutant mice.

Figure 3 shows RNase protection assay analysis of mouse GPR41 expression in mouse cell types and tissues.

Figure 4 shows coupling of GPR41 to G-protein G-alpha i.

Figure 5 shows coupling of GPR41 to G-protein G-alpha 12/13.

Figure 6 shows efficacy of GPR41 agonists in Gq/Gi co-transfected 293 cells.

Figure 7 shows a GPR41 agonist inhibits insulin release in MIN6 insulinoma cells.

Figure 8 shows that a GPR41 agonist, Compound 4, reverses the beneficial effect of an oral glucose tolerance test (oGTT) lowering compound, B111.

CLAIMS

We claim:

1. A method for identifying a glycemic stabilizing compound, comprising:

a) contacting a candidate compound with GPR41, and

b) determining whether GPR41 functionality is modulated,

wherein a modulation in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound.

2. The method of claim 1, wherein said GPR41 is human.

3. The method of claim 1, wherein said determining comprises a second messenger assay.

4. The method of claim 1, wherein said glycemic stabilizing compound comprises a compound selected from the group consisting of:

2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

5. A glycemic stabilizing compound identified according to the method of claim 1.

6. The compound of claim 5, wherein said glycemic stabilizing compound is a GPR41 agonist.

7. The compound of claim 6, wherein said glycemic stabilizing compound comprises a compound selected from the group consisting of:

2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, cyclopropanecarboxylic acid 4-[1,2,3]thiadiazol-4-yl-phenyl ester, cyclopropanecarboxylic acid; 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide, 4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide, 2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 5, wherein said glycemic stabilizing compound is a GPR41 inverse agonist or antagonist.

9. The compound of claim 8, wherein said glycemic stabilizing compound comprises a compound selected from the group consisting of:

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

10. A method for preparing a composition which comprises identifying a glycemic stabilizing compound and then admixing said compound with a carrier, wherein said compound is identified by the method of claim 1.

11. A pharmaceutical composition comprising, consisting essentially of, or consisting of the compound of claim 5.

12. A method for treating or preventing an insulin-related disorder in an individual in need thereof, comprising administering to said individual an effective amount of the compound of claim 11.

13. The method of claim 12, wherein said insulin-related disorder is hypoglycemia, an insulin-secreting or insulin-dependent tumor, aging, insulin resistance, impaired glucose tolerance, or diabetes.

14. The method of claim 12, further comprising administering to said individual an effective amount of an agent used for the treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of the compound of claim 11.

15. The method of claim 12, wherein the individual is a mammal.

16. The method of claim 12, wherein the individual is a human.

17. A method for the manufacture of a medicament comprising a compound of claim 11, for use as a glycemic stabilizing compound.

18. A method for the manufacture of a medicament comprising a compound of claim 11, for use in the treatment of an insulin-related disorder.

19. A method for identifying a glycemic stabilizing compound, comprising:

a) contacting a candidate compound with GPR41, and

b) determining whether GPR41 functionality is decreased,

wherein a decrease in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound.

20. The method of claim 19, wherein said GPR41 is human.

21. The method of claim 19, wherein said determining comprises a second messenger assay.

22. The method of claim 19, wherein said glycemic stabilizing compound comprises a compound selected from the group consisting of:

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-

oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

23. A glycemic stabilizing compound identified according to the method of claim 19.

24. The compound of claim 23, wherein said glycemic stabilizing compound is a GPR41 inverse agonist.

25. The compound of claim 23, wherein said glycemic stabilizing compound is a GPR41 antagonist.

26. The compound of claim 23, wherein said glycemic stabilizing compound comprises a compound selected from the group consisting of:

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

27. A method for preparing a composition which comprises identifying a glycemic stabilizing compound and then admixing said compound with a carrier, wherein said compound is identified by the method of claim 19.

28. A pharmaceutical composition comprising, consisting essentially of, or consisting of the compound of claim 23.

29. A method for treating or preventing an insulin-related disorder in an individual in need thereof, comprising administering to said individual an effective amount of the compound of claim 28.

30. The method of claim 29, wherein said insulin-related disorder is insulin resistance, impaired glucose tolerance, or diabetes.

31. The method of claim 29, further comprising administering to said individual an effective amount of an agent used for the treatment of diabetes, blood lipid disorders, or obesity in combination with an effective amount of the compound of claim 28.

32. A method for decreasing GPR41 function, comprising contacting GPR41 with an effective amount of a GPR41 inverse agonist or antagonist.

33. The GPR41 inverse agonist or antagonist of claim 32, wherein said inverse agonist or antagonist comprises a compound selected from the group consisting of:

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 4-(5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide, 2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, 2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and 4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide; or a pharmaceutically acceptable salt thereof.

34. A method for decreasing blood glucose levels in an individual in need thereof, comprising administering to the individual an effective amount of a GPR41 inverse agonist or antagonist.

35. A method for increasing insulin secretion in an individual in need thereof, comprising administering to the individual an effective amount of a GPR41 inverse agonist or antagonist.

CLAIMS

1. An in vitro method for identifying a glycemic stabilizing compound, comprising:

   a) contacting a candidate compound with GPR41, and

   b) determining whether GPR41 functionality is modulated,

   wherein a modulation in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound;
   said GPR41 having an amino acid sequence as shown in SEQ ID NO:2, or a variant or ortholog thereof, wherein said variant is an allelic variant, splice variant or conservative amino acid substitution variant of GPR41.

2. A method according to claims 1, wherein said variant retains the function of a polypeptide with the amino acid sequence as shown in SEQ ID NO:2.

3. A method according to claim 1, wherein said GPR41 is human.

4. A method according to claim 1, wherein said determining comprises a second messenger assay.

5. A glycemic stabilizing compound identified by the method according to claim 1 selected from the following compounds and pharmaceutically acceptable salts thereof:

   2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

   4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

   4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide,

   4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

   4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide,

   2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-((5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydroquinoline=3-carboxylic acid (2-chloro-phenyl)-amide,

2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and

4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide.

6. A compound according to claim 5, wherein said glycemic stabilizing compound is a GPR41 agonist.

7. A compound according to claim 6, wherein said glycemic stabilizing compound is a compound selected from the following compounds and pharmaceutically acceptable salts thereof:

2-methyl-4-(4-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2,5-dichloro-phenyl)-amide,

4-Furan-2-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-Furan-3-yl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (4-chloro-phenyl)-amide,

2-Methyl-4-(4-methylsulfanyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid o-tolylamide, and

2-Methyl-4-(3-nitro-phenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide.

8. A compound according to claim 5, wherein said glycemic stabilizing compound is a GPR41 inverse agonist or antagonist.

9. A compound according to claim 8, wherein said glycemic stabilizing compound comprises a compound selected from the following compounds and pharmaceutically acceptable salts thereof:

2-Methyl-4-[5-(2-nitro-4-trifluoromethyl-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

4-((5-Biphenyl-2-yl-furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-4-[5-(2-nitro-phenyl)-furan-2-yl]-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid (2-chloro-phenyl)-amide,

2-Methyl-5-oxo-4-(4-phenoxy-phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide,

2-Methyl-5-oxo-4-[5-(2-trifluoromethoxy-phenyl)-furan-2-yl]-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide, and

4-[5-(2,5-Dichloro-phenyl)-furan-2-yl]-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid o-tolylamide.

10. A method for preparing a composition comprising a glycemic stabilizing compound said method including admixing said compound with a carrier, wherein said compound is a compound according to any one of claims 5 to 9.

11. A pharmaceutical composition comprising, consisting essentially of, or consisting of a compound according to any one of claims 5 to 9.

12. A compound according to any one of claims 5 to 9 for use in a method of treatment of human or animal body by therapy.

13. A compound according to any one of claims 5 to 9 for use in a method of treatment of an insulin-related disorder.

14. Use of a compound according to any one of claims 5 to 9 in the manufacture of a medicament for the treatment of an insulin-related disorder.

15. A compound according to claim 5 for use in a method of treatment of hypoglycemia, an insulin-secreting or insulin-dependent tumor, insulin resistance, impaired glucose tolerance, or diabetes.

16. Use of a compound according to claim 5 in the manufacture of a medicament for the treatment of hypoglycemia, an insulin-secreting or insulin-dependent tumor, insulin resistance, impaired glucose tolerance, or diabetes.

17. A method according to any one of claims 1 to 4 wherein step b) comprises determining whether GPR41 functionality is decreased,
wherein a decrease in GPR41 functionality is indicative of the candidate compound being a glycemic stabilizing compound.

18. A method according to claim 17 wherein said glycemic stabilizing compound is capable of increasing insulin secretion.

19. A compound according to claim 12 for use in a method of treatment of the human body by therapy.