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(54) Title: METHOD OF USING CALCILYTIC COMPOUNDS TO TREAT DISEASES OF ABNORMAL GLUCOSE OR INSULIN LEVELS

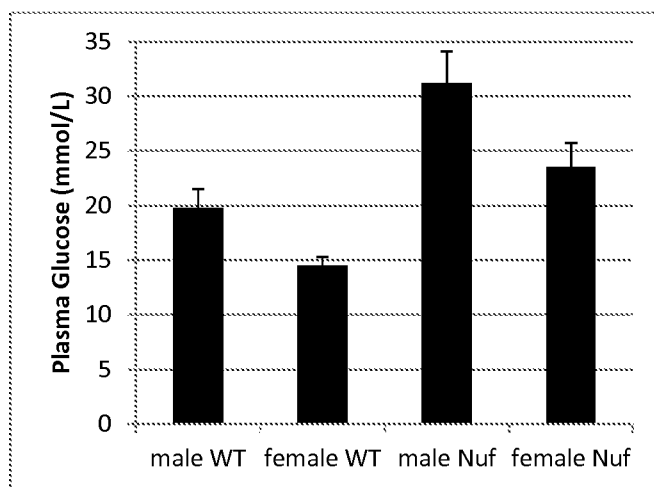


Figure 1

(57) Abstract: The disclosure includes a method to treat glucose intolerance and/or insulin resistance and associated symptoms by administering a calcilytic drug to a subject in need thereof.



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METHOD OF USING CALCILYTIC COMPOUNDS TO TREAT DISEASES OF ABNORMAL GLUCOSE OR INSULIN LEVELS

TECHNICAL FIELD

[0001] The present disclosure relates generally to methods of treating hyperglycemia, diabetes, metabolic syndrome or symptoms thereof. The method includes the step of administering a calcilytic drug to a subject presenting with glucose intolerance and/or insulin resistance.

BRIEF DESCRIPTION OF THE DRAWINGS

[0002] Figure 1 is a graph that illustrates plasma glucose levels in Nuf mice and wild-type littermates.

[0003] Figure 2 is a graph that illustrates plasma insulin levels in Nuf mice and wild-type littermates.

[0004] Figure 3 is a graph that illustrates plasma glucose levels in Nuf mice treated with either vehicle or the calcilytic, ronacaleret.

BRIEF SUMMARY

[0005] The present disclosure relates to methods of treating diseases of abnormal glucose or insulin levels, including diabetes, metabolic syndrome, or symptoms thereof, including the step of administering a calcilytic drug to a subject presenting with glucose intolerance. The cause of the disease may be hereditary or etiological. Moreover, the disease may be associated with a mutation in the calcium-sensing receptor (CaSR) or a mutation in one or more downstream participants in CaSR signaling. In some embodiments, the calcilytic drug may be administered to subjects with a gain of function mutation in either the CaSR or at least one of its downstream signaling molecules at either a reduced dose, a reduced frequency of dosing, or both relative to a subject that expresses the wild-type protein(s).

DETAILED DESCRIPTION

[0006] Types 1 and 2 diabetes and metabolic syndrome are diseases that are associated with glucose intolerance. These illnesses are accompanied by an increased risk of cardiovascular disease and other life-threatening disorders. Despite their severity, treatments for these diseases are limited.

[0007] The G-protein coupled calcium-sensing receptor (CaSR) is a pivotal regulator of extracellular calcium homeostasis. Calcilytics are molecules that block CaSR signaling. They antagonize CaSR signaling by directly interacting with the CaSR. The cells in which the CaSR is expressed include pancreatic beta cells, where it regulates insulin secretion *in vitro*. However, the role of this receptor in glucose homeostasis is unknown.

[0008] We disclose a method of treating hyperglycemia, diabetes, metabolic syndrome, or symptoms thereof, comprising the step of administering a calcilytic drug to a subject in need thereof. Such symptoms include, but are not limited to, glucose intolerance. The method includes treatment of subjects that express either wild-type or a variant CaSR.

Definitions

[0009] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in drug dosing and other techniques used to conduct the *in vivo* pharmacological experiments described below are those well-known and commonly employed in the art. Standard techniques, or modifications thereof, are used for plasma analysis.

[0010] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a buffer" includes a plurality of such buffers, reference to "the buffer" is a reference to one or more buffers and equivalents thereof known to those skilled in the art, and so forth. Similarly, for example, reference to "the method" includes reference to equivalent steps and methods known to those skilled in the art.

[0011] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed as a range, then 11, 12, 13, and 14 are also disclosed.

[0012] "Oral administration" as used herein, means administration of a therapeutic agent into the alimentary canal through the mouth. Oral compositions of the calcilytics for use in the disclosed methods may be formulated as syrups, tablets, capsules, and lozenges as well as other formulations known in the art.

[0013] "Parenteral administration" as used herein, means administration of a therapeutic

agent via intravenous injection or infusion, intravascular injection, subcutaneous injection, intraperitoneal injection, or intramuscular injection.

[0014] "Wild-type littermate" as used herein, means a littermate in a mouse litter that includes Nuf mouse littermates and which does not include a calcium-sensing receptor gene with the activating CaSR mutation, Leu723Gln, in its genome.

Calcilytic Compounds.

[0015] The methods described herein feature calcilytic compounds. "Calcilytic compounds" refer to compounds able to inhibit calcium receptor activity, including receptor antagonists. The ability of a compound to "inhibit calcium receptor activity" means that the compound causes a decrease in one or more calcium receptor activities evoked by extracellular Ca^{2+} . The use of calcilytic compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient is known, for example, from U.S. Patent Nos. 6,395,919, 7,202,261, and 7,829,594, each of which is incorporated herein in its entirety.

[0016] In many mammals, the concentration of extracellular ionized calcium (Ca^{2+}) (hereinafter, $[\text{Ca}^{2+}]_o$) is typically under rigid homeostatic control and regulates various processes such as blood clotting, nerve and muscle excitability, and proper bone formation. Serum Ca^{2+} concentration is kept within the relatively narrow range of about 1.1-1.4 mmol/L. Extracellular Ca^{2+} inhibits the secretion of parathyroid hormone ("PTH") from parathyroid cells, and stimulates secretion of calcitonin from C-cells. The CaSR enables certain specialized cells to respond to changes in $[\text{Ca}^{2+}]_o$. These specialized cells include pancreatic beta cells which secrete insulin. It has been shown that insulin secretion is modified in response to variations in $[\text{Ca}^{2+}]_o$. This is thought to occur through a mechanism that involves cell-cell communication between pancreatic beta cells that occurs in response to local increases in $[\text{Ca}^{2+}]_o$ rather than changes in systemic calcium concentrations.

[0017] Calcilytic drugs, through their ability to inhibit CaSR activity, thereby cause a decrease in one or more CaSR activities evoked by extracellular Ca^{2+} . Such compounds are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides such as hormones, enzymes or growth factors, the expression and/or secretion of which is regulated or affected by activity at the CaSR.

[0018] Abnormal calcium homeostasis may be characterized by one or more of the following activities: an abnormal increase or decrease in serum calcium; an abnormal increase or decrease in urinary excretion of calcium; an abnormal increase or decrease in bone calcium levels (for example, as assessed by bone mineral density measurements); an abnormal absorption of dietary calcium; an abnormal increase or decrease in the production

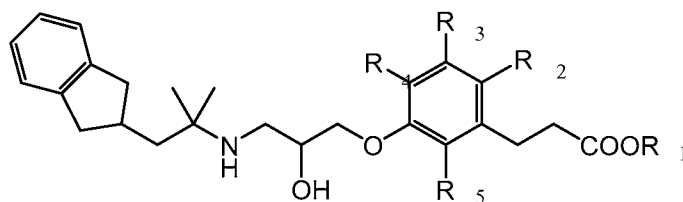
and/or release of messengers which affect serum calcium levels, such as PTH and calcitonin; and an abnormal change in the response elicited by messengers which affect serum calcium levels.

[0019] CaSR inhibitors are important in the pharmacotherapy of diseases associated with abnormally low levels of serum calcium such as hypoparathyroidism and idiopathic hypercalciuria and may be used to treat other disorders of bone and mineral metabolism/homeostasis such as osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, and osteoporosis.

[0020] In addition to the aforementioned disorders that are known to be associated with abnormal calcium homeostasis, we provide evidence that diseases associated with abnormal serum glucose levels are associated with elevated calcium levels and/or excessive CaSR signaling. We further provide evidence that these disorders may be treated by administering drugs that antagonize the CaSR. Such disorders include, but are not limited to, type 1 diabetes, type 2 diabetes, gestational diabetes, pre-diabetes, metabolic syndrome, and others associated with glucose intolerance and/or insulin resistance.

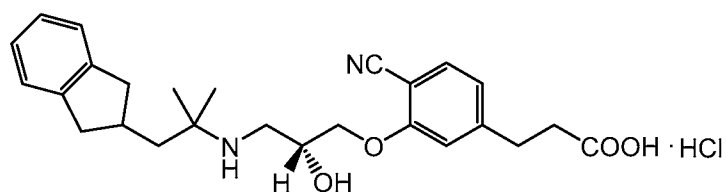
[0021] It has been reported that CaSR activators, called calcimimetics, transiently increase insulin secretion in human and rodent pancreatic beta cells. Gray et al., (2006), *J. Endocrinol.* **190**, 703–710. Consequently, the experimental results disclosed herein showing that a calcilytic reduced plasma glucose levels in a hypocalcemic/hyperglycemic mouse model are surprising and paradoxical.

[0022] Calcilytic compounds that may be used in the disclosed methods include those of Formula (I), shown below. In certain embodiments, the R groups are alkyl or hydrogen.



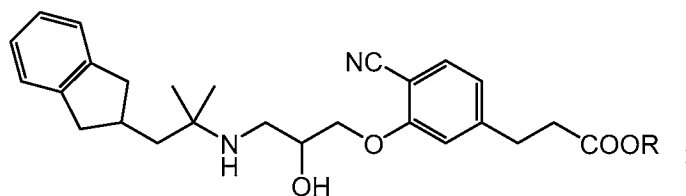
Formula (I)

[0023] The compound referred to herein as Compound 1 has the structure of Formula (I) where R₁, R₂, R₃, and R₅ are H, and R₄ is a nitrile group. Compound 1 has the chemical name of (R)-3-(4-cyano-3-(3-(1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-ylamino)-2-hydroxypropoxy) phenyl) propanoic acid, the structure of which is shown below.



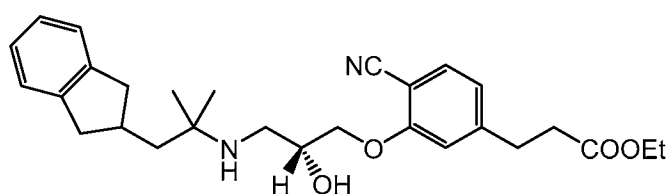
Compound 1

[0024] In certain embodiments, the calcilytic drug of the disclosed methods is an ester, having the structure of Formula (I) where R_1 is an alkyl group such as methyl or ethyl. Alternatively, Compound 1 may be a prodrug. In some instances, the R_1 group may be involved in the conversion of the prodrug to the active compound. Such embodiments have the structure of Formula (II), shown below.



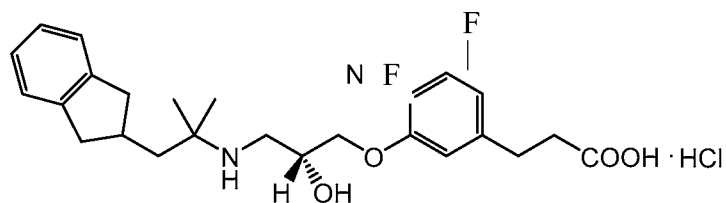
Formula (II)

[0025] One species of Formula (II) which may be used in the disclosed methods is the compound referred to herein as Compound 2. As shown below, Compound 2 has the structure of Formula (II) in which R_1 is an ethyl and has the chemical name of ethyl (R)-3-(4-cyano-3-(3-((1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-yl)amino)-2-hydroxypropoxy)phenyl)propanoate.



Compound 2

[0026] In another embodiment, the calcilytic compound used in the disclosed methods comprises ronacaleret, which has the chemical name of 3-[3-[(2R)-3-[1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]-4,5-difluorophenyl]propanoic acid, the structure of which is shown below.



Ronacaleret

[0027] As evidenced by their structures shown above, Compound 1 and ronacaleret include a carboxylic acid moiety. Such acids may be isolated or prepared in a salt form. A pharmaceutically acceptable salt includes a salt formed from an inorganic acid such as a hydrobromide or hydrochloride salt. The stoichiometry of the salt may be, for example, a hemi-salt, or a mono- or di-salt or tri-salt.

[0028] In addition to salt forms, the present disclosure includes calcilytic compounds which may be in a prodrug form. Prodrugs of the calcilytic compounds described herein readily undergo chemical changes under physiological conditions to provide the calcilytic compounds.

[0029] Certain calcilytic drugs can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure. Some calcilytic drugs may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are within the scope of the present disclosure.

[0030] Calcilytic drugs encompassed by the present disclosure include all isotopes of atoms occurring therein. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. As is evident from the structure of Formulae (I) and (II), some calcilytic drugs possess chiral or asymmetric carbon atoms (optical centers); the racemates, diastereomers, geometric isomers and individual optical isomers are all intended to be encompassed within the scope of the present invention.

[0031] It should be noted that embodiments of methods comprising the step of administering a calcilytic drug to treat or prevent one or more of the disclosed indications are presented herein for purposes of example only and not for purposes of limitation. In particular embodiments, the methods disclosed herein comprise the step of oral, parenteral, topical (transdermal), oral inhalation, or transmucosal administration of the calcilytic. In

particular embodiments, the calcilytic is administered orally. In related embodiments, the calcilytic is administered parenterally.

[0032] Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/kg, and preferably from 0.1 to 50 mg/kg body weight, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/kg body weight, of a compound of Formula(I) or Formula (II). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I) or Formula (II). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art. As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

[0033] In another embodiment, the method may be used to treat diseases of abnormal glucose or insulin levels, including diabetes, metabolic syndrome, or symptoms thereof in patients that possess a genetic mutation that results in a modified CaSR protein. In some instances, the modified CaSR may exhibit increased sensitivity to extracellular calcium relative to the wild-type CaSR. Furthermore, the modified CaSR protein may comprise a missense mutation, a deletion in the CaSR protein, or both. Examples of CaSR protein mutations that may be present in patients suffering from diseases which may be treated by administering calcilytic drugs according to the methods disclosed herein include one or more of Lys29Glu, Leu125Pro, Cys131Trp, Glu228Ala, Asp410Glu, Leu723Glu, Ala840Val, Ala843Glu and any of the 90 unique mutations (86 missense, 3 frame-shifts, 1 deletion) identified to date (Hannan et al. 2012 *Human Molecular Genetics* 21:2768-2778, which is herein incorporated by reference).

[0034] An effective amount of a calcilytic drug for treatment of hyperglycemia, diabetes, metabolic syndrome, or symptoms thereof would have one or more of the following effects: reduced serum calcium, reduced urinary calcium excretion, increased serum parathyroid hormone, reduced plasma glucose, and increased plasma insulin.

[0035] Amino alcohol calcilytic drugs (Formula I and II) interact with the CaSR within the transmembrane domain of the receptor. Mutations in the CaSR that are located near the amino alcohol calcilytic binding site include Leu723Glu, Ala840Val, and Ala843Glu. Because patients with altered plasma glucose and/or insulin levels may express a CaSR gene with a mutation that results in an altered CaSR protein, the amount of calcilytic drug required to reduce elevated plasma glucose, raise abnormally low plasma insulin levels, and mitigate

related symptoms as discussed herein, may be altered relative to that necessary to cause these effects in an individual that expresses the wild-type CaSR. In one embodiment, the disclosed method is used to treat a patient that possesses a genetic mutation that results in a gain of function in the CaSR protein. For example, the disclosed method may be used to treat such a patient by administering a lower dose of calcilytic drug relative to that required to treat an individual that expresses the wild-type CaSR. Alternatively, the dosing frequency that is effective to mitigate these symptoms in a patient that expresses an altered CaSR protein may be altered relative to that necessary to cause the same or similar effects in an individual that expresses the wild-type CaSR. In one embodiment, the dosing frequency is reduced in a patient that expresses an altered CaSR protein that includes a gain of function mutation relative to that necessary to cause the same or similar effects in an individual that expresses the wild-type CaSR. Furthermore, both the effective dose and effective dosing schedule may be altered in an individual that expresses a modified CaSR protein. For example, both the effective dose and the effective dosing frequency necessary to cause the aforementioned effects may be reduced when treating an individual that expresses a CaSR protein with a gain of function mutation as compared to an individual that expresses the wild-type CaSR.

[0036] As a result of inhibiting CaSR signaling, the step of administering a calcilytic drug to a patient may alter the expression of genes downstream of CaSR signaling to levels that occur in the presence of lowered extracellular calcium. Consequently, the disclosed method includes the step of administering a calcilytic drug wherein serum parathyroid hormone and/or fibroblast growth factor-23 levels are elevated.

Methods of Treating Subjects with a Calcilytic Drug

[0037] The methods of treating subjects with the calcilytic drugs as described herein include administration by different routes, including, without limitation, intravenous, intravascular, intraperitoneal, subcutaneous, intramuscular, topical (transdermal), transmucosal, and oral administration. For oral administration, the compounds may be formulated into oral dosage forms such as, for example, liquid-filled capsules, or liquid preparations such as syrups, elixirs, or concentrated drops. For injection, the calcilytic drugs may be formulated in isotonic liquid solutions, such as in physiologically compatible buffers or carbohydrate solutions. Intravenous, subcutaneous, intraperitoneal, and intramuscular doses may be given by means of a bolus injection. Alternatively the intravenous or intraperitoneal dose may be given by continuous infusion over a period of time.

[0038] The invention is illustrated further by the following example, which is not to be construed as limiting the invention in scope of the specific procedures described therein.

Example

[0039] We investigated a hypocalcemic mouse model, known as Nuf, with an activating CaSR mutation (Leu723Gln) to determine whether abnormal CaSR function *in vivo* affects glucose tolerance, and to assess whether a CaSR-targeted drug may rectify any alterations of plasma glucose concentrations. The Nuf mouse origin and phenotype is described by Hough et al., (2004), *Proc. Natl. Acad. Sci. U. S. A.* **101**, 13566-71. All studies were conducted in accordance with institutional welfare guidelines. A glucose tolerance test was performed by administering a 2g/kg intraperitoneal glucose bolus to fasted mice (N=6-9 mice per group) and collecting blood samples at 0 and 30 minutes. Plasma glucose and insulin concentrations were measured using an Analox glucose analyser and Milliplex mouse immunoassay, respectively. Glucose tolerance testing revealed adult homozygous male and female Nuf mice (*Nuf/Nuf*) to have significantly raised plasma glucose concentrations (male glucose = 31.2 ± 2.9 vs 19.8 ± 1.7 mmol/L, $P < 0.01$; female glucose = 23.5 ± 2.2 vs 14.5 ± 0.8 mmol/L, $P < 0.01$; shown in Figure 1) and reduced plasma insulin concentrations (male insulin = 0.50 ± 0.03 vs 0.85 ± 0.08 ng/mL, $P < 0.01$; female insulin = 0.54 ± 0.05 vs 0.74 ± 0.05 ng/mL, $P < 0.01$; shown in Figure 2) when compared to wild-type littermates at 30 minutes. We next evaluated the effect of the selective CaSR antagonist ronacaleret on the impaired glucose tolerance of Nuf mice. A dose ranging study demonstrated that 90 mg/kg of ronacaleret administered twice daily by oral gavage over 5 days was tolerated by Nuf mice and successfully increased plasma calcium concentrations. Age-matched male and female Nuf mice were randomized to receive either ronacaleret or drug vehicle (N=7-11 mice per group) using the 90 mg/kg dosing regimen. Administration of ronacaleret over 5 days successfully lowered plasma glucose concentrations in male and female *Nuf/Nuf* mice (male treatment group glucose = 21.4 ± 3.0 vs 32.8 ± 2.9 mmol/L, $P < 0.05$; female treatment group glucose = 13.7 ± 1.9 vs 18.1 ± 1.8 mmol/L, $P < 0.05$) compared to *Nuf/Nuf* mice receiving drug vehicle only (see Figure 3). Thus, ronacaleret-treated Nuf mice displayed glucose concentrations that were not significantly different from wild-types. These findings demonstrate that the CaSR is a determinant of glucose homeostasis and novel target for the modulation of plasma glucose concentrations.

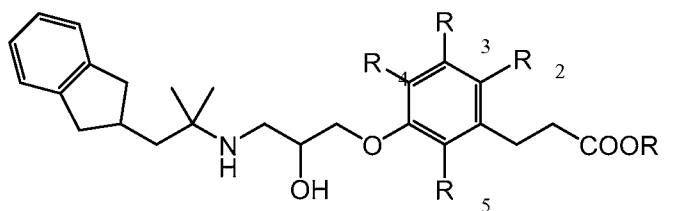
[0040] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein and as though fully set forth.

[0041] Modifications and improvements of the embodiments specifically disclosed herein

are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the area can, using the preceding description, utilize the present disclosure to its fullest extent. Therefore, the embodiments disclosed herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments disclosed in which an exclusive property or privilege is claimed are defined as follows.

Claims:

1. A method for treating impaired glucose tolerance, insulin resistance, or symptoms thereof, comprising the step of administering an effective amount of a calcilytic drug to a subject in need thereof.
2. The method according to claim 1, wherein the calcilytic consists of a compound according to the formula:

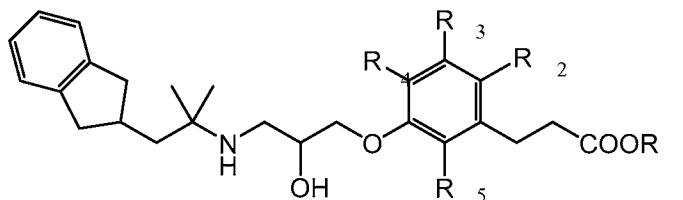


wherein R is either an alkyl or hydrogen.

3. The method according to claim 1, wherein the calcilytic is selected from the group that consists of (R)-3-(4-cyano-3-(3-(1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-ylamino)-2-hydroxypropoxy) phenyl) propanoic acid, ethyl (R)-3-(4-cyano-3-(3-((1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-yl)amino)-2-hydroxypropoxy)phenyl)propanoate, and ronacaleret.
4. The method according to claim 1, wherein the calcilytic drug is an amino alcohol.
5. The method according to claim 1, wherein the calcilytic drug consists of ronacaleret.
6. The method according to claim 1, wherein the calcilytic drug is administered by one or more of oral, parenteral, topical, nasal or oral inhalation, or transmucosal methods .
7. The method according to claim 1, wherein the glucose intolerance or insulin resistance is associated with one or more of prediabetes, gestational diabetes, type 1 diabetes, type 2 diabetes, or metabolic syndrome.
8. The method according to claim 1, wherein the calcilytic drug is administered within a dose range of about 0.01 mg/kg to about 500 mg/kg body weight.
9. The method according to claim 8, wherein the calcilytic drug is administered within a dose range of about 0.1 mg/kg to 50 mg/kg body weight.

10. A method for treating impaired glucose tolerance, insulin resistance, or symptoms thereof, comprising the step of administering an effective amount of a calcilytic drug to a subject in need thereof, wherein the subject comprises a genetic mutation in a calcium sensing receptor gene.
11. The method according to claim 10, wherein the genetic mutation encodes for a modified calcium sensing receptor protein.
12. The method of claim 11, wherein the calcium sensing receptor comprises increased sensitivity to extracellular calcium relative to the wild-type calcium sensing receptor.
13. The method according to claim 11, wherein the modified calcium sensing receptor protein comprises a deletion.
14. The method according to claim 11, wherein the genetic mutation is a missense mutation.
15. The method according to claim 14, wherein the missense mutation comprises at least one of the group that consists of Lys29Glu, Leu125Pro, Cys131Trp, Glu228Ala, Asp410Glu, Leu723Glu, Ala840Val, and Ala843Glu.
16. The method according to claim 10, wherein the effective amount of the calcilytic is altered relative to that which is required to inhibit signaling of the wild-type calcium sensing receptor in a subject.
17. The method according to claim 16, wherein the effective amount of the calcilytic is reduced relative to that which is required to inhibit signaling of the wild-type calcium sensing receptor in a subject.
18. The method according to claim 10, wherein the calcilytic is administered at a dosing frequency that is altered relative to that which is required to inhibit signaling of the wild-type calcium sensing receptor in a subject.
19. The method according to claim 18, wherein the dosing frequency is reduced relative to that which is required to inhibit signaling of the wild-type calcium sensing receptor in a subject.
20. A method according to claim 10, wherein expression of genes downstream of the calcium sensing receptor respond as if extracellular calcium levels had been lowered.

21. The method according to claim 10, wherein the calcilytic consists of a compound according to the formula:



wherein R is either an alkyl or hydrogen.

22. The method according to claim 10, wherein the calcilytic is selected from the group that consists of (R)-3-(4-cyano-3-(3-(1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-ylamino)-2-hydroxypropoxy) phenyl) propanoic acid, ethyl (R)-3-(4-cyano-3-(3-((1-(2,3-dihydro-1H-inden-2-yl)-2-methylpropan-2-yl)amino)-2-hydroxypropoxy)phenyl)propanoate, and ronacaleret.
23. The method according to claim 10, wherein the calcilytic drug is an amino alcohol.
24. The method according to claim 10, wherein the calcilytic drug consists of ronacaleret.
25. The method according to claim 10, wherein the calcilytic drug is administered by one or more of oral, parenteral, topical, nasal or oral inhalation, or transmucosal methods .
26. The method according to claim 10, wherein the glucose intolerance or insulin resistance is associated with one or more of prediabetes, gestational diabetes, type 1 diabetes, type 2 diabetes, or metabolic syndrome.

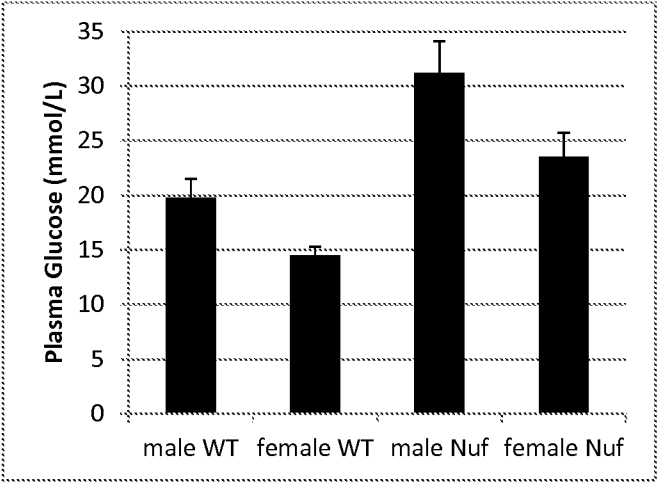


Figure 1

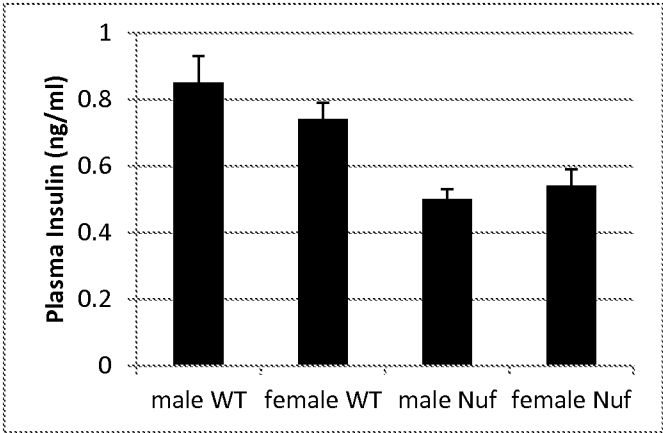


Figure 2

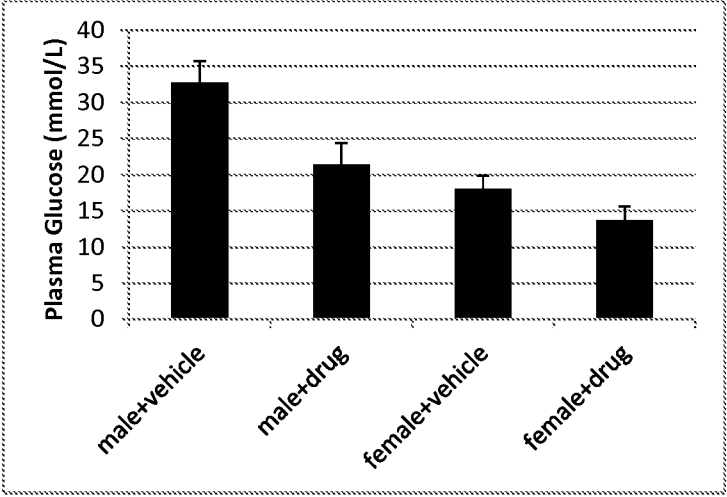


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/37010

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 213/00 (2015.01)

CPC - C07D 213/38; C07D 213/61; C07D 213/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): C07D 213/00

CPC: C07D 213/38; C07D 213/61; C07D 213/42

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 546/329, 549/492, 549/74, 546/229Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Keyword limited: Calcilytic, calcimimetic, calcilytic compounds, calcium sensing receptor, calcium sensing receptor gene, abnormal glucose/insulin, prediabetic, gestational diabetes, ronacaleret, amino alcohol, calcium sensing receptor gene mutation/missense/nonsense

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0163589 A1 (MARQUIS, RW et al.) 25 June 2009 (25.06.2009), entire document, especially: abstract; para [0003]; para [0005]; para [0009]; para [0013], Structure I; para [0026]; Example 2; para [0040]; 3-(3,4-Difluoro-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid hydrochloride; para [0034], Scheme 1, compound 8.	1-26
Y	US 2011/0229587 A1 (NEULS, D) 22 September 2011 (22.09.2011), entire document, especially: abstract; para [0002]; para [0006]; para [0012].	1-26
Y	US 2007/0155819 A1 (MARQUIS, RW et al.) 05 July 2007 (05.07.2007), entire document, especially: abstract; para [0001]; para [0008]; para [0060]; para [0061]; para [0062]; para [0063]; para [0066]; para [0067]; para [0076]; para [0078].	6,8-9, 25
Y	NAKAMURA, A et al. "Loss-of-Function and Gain-of-Function Mutations of Calcium-Sensing Receptor: Functional Analysis and the Effect of Allosteric Modulators NPS R-568 and NPS-2143", J Clin Endocrinol Metab. 2013. Vol 98(10), pp E1692?E1701, entire document, especially: abstract; pg E1693, col 1, para 2; pg E1693, col 2, para 5; pg E1694, col 2, para 3; Figure 3D-F.	10-26
A	US 2013/0190407 A1 (VAN WAGENEN, BC et al.) 25 July 2013 (25.07.2013), entire document	1-26

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 August 2015 (26.08.2015)

Date of mailing of the international search report

18 SEP 2015

Name and mailing address of the ISA/US

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