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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

[Continued on next page]

(54) Title: NOVEL GLUCAGON-LIKE PEPTIDE 1 MODULATOR AND USES THEREOF

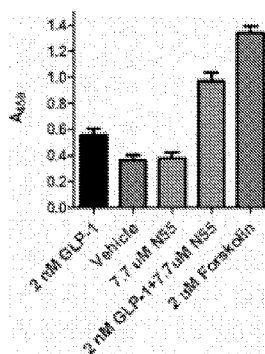


FIG 4

(57) Abstract: Disclosed herein are novel glucagon-like peptide-1 (GLP-1) modulators and their uses in manufacturing medicaments for the treatment and/or prophylaxis of diseases and/or disorders associated with hyperglycemia.



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NOVEL GLUCAGON-LIKE PEPTIDE 1 MODULATOR AND USES THEREOF**CROSS REFERENCES**

[0001] This application claims priority to U.S. Provisional Application No.
5 62/186512, filed June 30, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] 1. FIELD OF THE INVENTION

[0003] The present disclosure in general relates to the field of treatment of
10 hyperglycemia; more particularly to the novel glucagon like peptide 1 modulators, and their uses in the treatment or prophylaxis of diseases and/or disorders associated with hyperglycemia.

[0004] 2. DESCRIPTION OF RELATED ART

[0005] High blood sugar (or hyperglycemia) is a condition in which an excessive
15 amount of glucose circulates in the blood plasma. Hyperglycemia is most commonly caused by diabetes mellitus that is increasingly prevalent and results in a high frequency of complications that lead to a significant reduction of life quality and expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause of
20 adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a 2 to 5 folds increase in cardiovascular disease risk. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Diabetes has also been implicated in the development of kidney
25 disease and with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes-associated complications are among the leading causes of morbidity and mortality worldwide.

[0006] "Good glycemic control" is characterized by maintaining blood glucose
30 levels within acceptable limits and by minimizing fluctuations outside of normal

limits between treatments. Persistent poor glycemic control increases the risk of long-term vascular complications of diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, neuropathy (loss of sensation, especially in the feet), and gangrene. Poor glycemic control also
5 increases the risk of short-term complications of surgery such as poor wound healing.

[0007] Traditional therapeutic drugs for the treatment of type-2 diabetes, such as metformin, sulfonylureas or insulin, do not always provide good glycemic control. Two new drug classes have been developed: glucagon-like peptide
10 (GLP)-1 receptor (GLP-1R) agonist, and dipeptidyl peptidase 4 (DPP-4) inhibitor. Currently, two GLP-1R agonists are available, they are exenatide and liraglutide, with several more currently being developed. DPP-4 inhibitor class exemplified by sitagliptin, alogliptin, and saxagliptin.

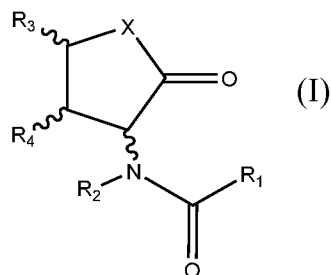
[0008] Although these therapeutic drugs can bring blood glucose levels within
15 normal limits in many patients with hyperglycemia, there are many patients with poor glycemic control and are in need of alternative treatment. Therefore, there is an unmet medical need for new therapeutic agents with new mechanisms of action, that are safe and effective for improving glycemic control in patients with hyperglycemia.

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SUMMARY

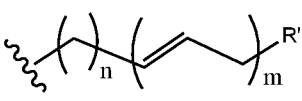
[0009] The present disclosure is based on unexpected discovery that certain compounds are potent GLP-1 receptor (GLP-1R) modulators that bind to GLP-1 and enhance the activation of GLP-1R signaling, these compounds are thus
25 useful for the development of medicaments for treating diseases and/or disorders associated with hyperglycemia (*e.g.*, type 2 diabetes, obesity and etc.).

[0010] Accordingly, one aspect of the present disclosure is to provide a novel compound having the structure of formula (I),
30



wherein:

X is O or S;

R₁ is H or  ;

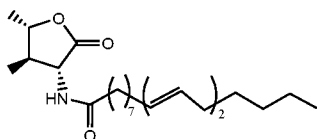
5 R₂ is H or a nitrogen protecting group;

R₃ and R₄ are independently H, halogen, optionally substituted alkyl or alkenyl; or R₃ and R₄ are taken together to form an optionally substituted 6-membered carbocycle or heterocycle;

R' is H or optionally substituted alkyl; and

10 n and m are independently an integral between 1 to 10.

[0011] According to one preferred embodiment, the compound of formula (I) is



[0012] A further aspect of the present disclosure is to provide a pharmaceutical
 15 composition for the treatment or prophylaxis of a subject having or suspected of having diseases and/or disorders associated with hyperglycemia. The pharmaceutical composition comprises a therapeutically or prophylactically effective amount of the compound of formula (I); and a pharmaceutically acceptable carrier.

20 [0013] The compound of formula (I) is present at a level of about 0.1% to 99% by weight, based on the total weight of the pharmaceutical composition. In some embodiments, the compound of formula (I) is present at a level of at least 1% by weight, based on the total weight of the pharmaceutical composition. In

certain embodiments, the compound of formula (I) is present at a level of at least 5% by weight, based on the total weight of the pharmaceutical composition. In still other embodiments, the compound of formula (I) is present at a level of at least 10% by weight, based on the total weight of the pharmaceutical composition. In still yet other embodiments, the compound of formula (I) is present at a level of at least 25% by weight, based on the total weight of the pharmaceutical composition.

[0014] According to some preferred embodiments, the pharmaceutical composition further comprises a blood sugar reducing agent, which is selected from the group consisting of, alpha-glucosidase inhibitor, biguanide, dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor, sulfonylurea, and thiazolidinedione.

[0015] The present disclosure also encompasses a method for the treatment or prophylaxis of a subject having or suspected of having a disease and/or disorder associated with hyperglycemia. The method comprises the step of administering a therapeutically or prophylactically effective amount of the compound of formula (I) to the subject, so as to ameliorate, mitigate and/or prevent the symptoms of the disease and/or disorder.

[0016] According to some preferred embodiments, the method further includes the step of administering to the subject another agent that is known to reduce the blood sugar level in the subject, such as an alpha-glucosidase inhibitor, biguanide, dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor, sulfonylurea, and thiazolidinedione, before, together with, or after the administration of the compound of formula (I) of the present invention.

[0017] The present disclosure also encompasses kits useful for the treatment or prophylaxis of a subject having or suspected of having a disease and/or disorder associated with hyperglycemia. The kit include, at least, a first container containing a blood sugar reducing agent; and a second container containing the present compound of formula (I).

[0018] The details of one or more embodiments of this disclosure are set forth in the accompanying description below. Other features and advantages of the invention will be apparent from the detail descriptions, and from claims.

[0019] It is to be understood that both the foregoing general description and the following detailed description are by examples, and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate various example systems, methods and other exemplified embodiments of various aspects of the invention. The present description will be better understood from the following detailed description read in light of the accompanying drawings, where,

[0021] FIG 1A illustrates the effect of compound 1 enhancing GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure;

[0022] FIG 1B illustrates the effect of compound 12 enhancing GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure;

[0023] FIG 1C illustrates the effect of a racemic mixture of compounds 16 and 17 enhancing GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure;

[0024] FIG 1D illustrates the effect of compound 14 enhancing GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure;

[0025] FIG 1E illustrates the effect of compound 18 enhancing GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure;

[0026] FIG 2 illustrates the effect of compound 1 (N55) on GLP-1 induced cAMP production in RINm5F cells in according to one embodiment of the present disclosure, (A) Increasing concentration of compound 1 (N55) on cAMP

production in response to GLP-1. (B) Compound 1 dose dependently and saturably increases the potency of GLP-1 to stimulate the production of cAMP; [0027] FIG 3 illustrates the effect of compound 1 on GLP-1 induced GLP-1R endocytosis in according to one embodiment of the present disclosure.

5 (A)Response of GLP-1R endocytosis to the titration of GLP-1 in the absence (circles) or presence (triangles) of 7.7 μ M of compound 1. (B) Compound 1 dose-dependently and saturably enhanced GLP-1R endocytosis elicited by 1 nM GLP-1;

[0028] FIG 4 illustrates the effect of compound 1 on GLP-1 elicited insulin
10 release from RINm5F cells in according to one embodiment of the present disclosure; and

[0029] FIG 5 illustrates the cytotoxicity test of compound 1 in accordance with one embodiment of the present disclosure.

15 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0030] The detailed description provided below in connection with the appended drawings is intended as a description of the present disclosure and is not intended to represent the only forms in which the present disclosure may be constructed or utilized.

20 [0031] 1. Definitions

[0032] Unless otherwise indicated, the term “alkyl” means a straight or branched hydrocarbon having from 1 to 23 carbon atoms, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 23 carbon atoms. Unless otherwise specified, each instance of an alkyl group is independently optionally
25 substituted, *i.e.*, unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents.

[0033] Unless otherwise indicated, the term “alkenyl” means a straight or branched hydrocarbon having from 2 to 23 carbon atoms (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 carbon atoms), and
30 including one or more carbon-carbon double bond (*e.g.*, 1, 2, 3, 4, 5, 6, or 7 carbon-carbon double bonds). The one or more carbon-carbon double bonds

can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents. In certain
5 embodiments, the alkenyl group is C₁₅ alkenyl having one carbon-carbon double bond. In certain embodiments, the alkenyl group is C₁₇ alkenyl having 2 or 3 carbon-carbon double bonds. In certain embodiments, the alkenyl group is C₁₉ alkenyl having 4 or 5 carbon-carbon double bonds. In certain embodiments, the alkenyl group is C₂₁ alkenyl having 6 carbon-carbon double bonds.

10 [0034] Unless otherwise indicated, the term “carbocycle” means a cycloalkyl or cycloalkenyl moiety. In certain embodiment, the carbocycle is a cyclohexyl moiety.

[0035] Unless otherwise indicated, the term “heterocycle” means a cycloalkyl or cycloalkenyl moiety wherein at least one of its carbon atoms has been replaced
15 with a heteroatom (*e.g.*, N, O or S). Examples include, but are not limited to, benzofuranyl, benzothienyl, quinolyl, benzodioxolyl, furyl, and thienyl.

[0036] Unless otherwise indicated, the terms “halogen” and “halo” encompass fluoro, chloro, bromo, and iodo.

[0037] Unless otherwise indicated, the term “substituted,” when used to
20 describe a chemical structure or moiety, refers to a derivative of that structure or moiety wherein one or more of its hydrogen atoms is substituted with an atom, chemical moiety or functional group such as, but not limited to, -OH, -CHO, alkoxy, alkanoyloxy (*e.g.*, -OAc), alkenyl, alkyl (*e.g.*, methyl, ethyl, propyl, t-butyl), aryl, aryloxy, halo, or haloalkyl (*e.g.*, -CCl₃, -CF₃, -C(CF₃)₃). Unless otherwise
25 indicated, the term “alkoxy” means an -O-alkyl group. Examples of alkoxy groups include, but are not limited to, -OCH₃, -OCH₂CH₃, -O(CH₂)₂CH₃, -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, and -O(CH₂)₅CH₃. The term “lower alkoxy” refers to -O-(lower alkyl), such as -OCH₃ and -OCH₂CH₃.

[0038] Unless otherwise indicated, “nitrogen protecting group” includes, but is
30 not limited to, alkyl, alkenyl, alkynyl, -OH, -OR^a, -C(=O)R^a, -CO₂R^a, -SOR^a, -SO₂R^a, and -SO₂OR^a, in which R^a refers to alkyl, alkenyl, aryl, aralkyl,

carbocycle, heterocycle, or heteroaryl. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd Edition, John Wiley & Sons, 1999, which is incorporated herein by reference.

5 [0039] Unless otherwise indicated, one or more adjectives immediately preceding a series of nouns is to be construed as applying to each of the nouns. For example, the phrase “optionally substituted alky, alkenyl, carbocycle or heterocycle” has the same meaning as “optionally substituted alky, optionally substituted alkenyl, optionally substituted carbocycle, or optionally substituted
10 heterocycle.”

[0040] For purpose of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituents as described herein which satisfy the valencies of the heteroatoms and result in the formation of a stable moiety.

15 [0041] Unless otherwise indicated, a “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A therapeutically effective amount of a compound is an amount of therapeutic agent, alone or in
20 combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

25 [0042] Unless otherwise indicated, a “prophylactically effective amount” of a compound is an amount sufficient to prevent a disease or condition, or one or more symptoms associated with the disease or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which
30 provides a prophylactic benefit in the prevention of the disease. The term “prophylactically effective amount” can encompass an amount that improves

overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0043] Unless otherwise indicated, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a patient is suffering from the specified
5 disease or disorder, which reduces the severity of the disease or disorder, or one or more of its symptoms, or retards or slows the progression of the disease or disorder.

[0044] It should also be noted that if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the
10 structure or the portion of the structure is to be interpreted as encompassing all stereoisomers of it. Similarly, names of compounds having one or more chiral centers that do not specify the stereochemistry of those centers encompass pure stereoisomers and mixtures thereof. Moreover, any atom shown in a drawing with unsatisfied valences is assumed to be attached to enough hydrogen atoms
15 to satisfy the valences.

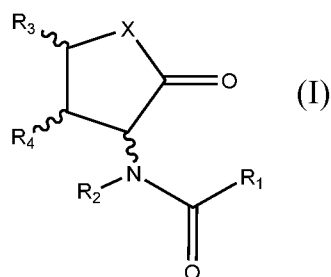
[0045] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily
20 resulting from the standard deviation found in the respective testing measurements. Also, as used herein, the term “about” generally means within 10%, 5%, 1%, or 0.5% of a given value or range. Alternatively, the term “about” means within an acceptable standard error of the mean when considered by one of ordinary skill in the art. Other than in the operating/working examples, or
25 unless otherwise expressly specified, all of the numerical ranges, amounts, values and percentages such as those for quantities of materials, durations of times, temperatures, operating conditions, ratios of amounts, and the likes thereof disclosed herein should be understood as modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical
30 parameters set forth in the present disclosure and attached claims are approximations that can vary as desired. At the very least, each numerical

parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0046] The singular forms “a”, “and”, and “the” are used herein to include plural referents unless the context clearly dictates otherwise.

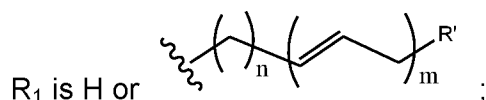
5 [0047] **2. Novel compounds of formula (I)**

[0048] This invention encompasses compounds of formula (I),



wherein:

10 X is O or S;



R₂ is H or a nitrogen protecting group;

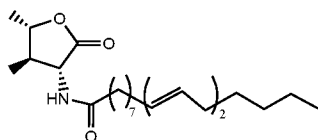
R₃ and R₄ are independently H, halogen, optionally substituted alkyl or alkenyl; or R₃ and R₄ are taken together to form an optionally substituted carbocycle or heterocycle;

15

R' is H or optionally substituted alkyl; and

n and m are independently an integral between 1 to 10.

[0049] According to one preferred embodiment, the compound of formula (I) is



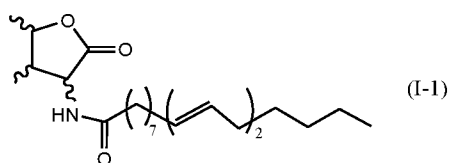
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[0050] Compounds of the invention contain one or more stereocenters, thus can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention thus encompasses stereomerically pure forms of such

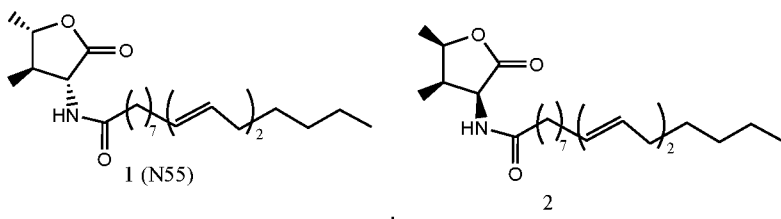
compounds, as well as mixtures of those forms. Stereoisomers may be asymmetrically synthesized or resolved using standard techniques such as crystallization, chromatography, and the use of a resolving agent. One preferred way of separating enantiomers from a racemic mixture is by use of preparative high performance liquid chromatography (HPLC). Alternatively, the racemic may be separated into its enantiomers by reacting with an optically active form of a resolving agent in the presence of a solvent. Depending on the optical form of the resolving agent, one of the two enantiomers is separated out as an insoluble salt with high yield and high optical purity, while the opposite enantiomer remains in the solution.

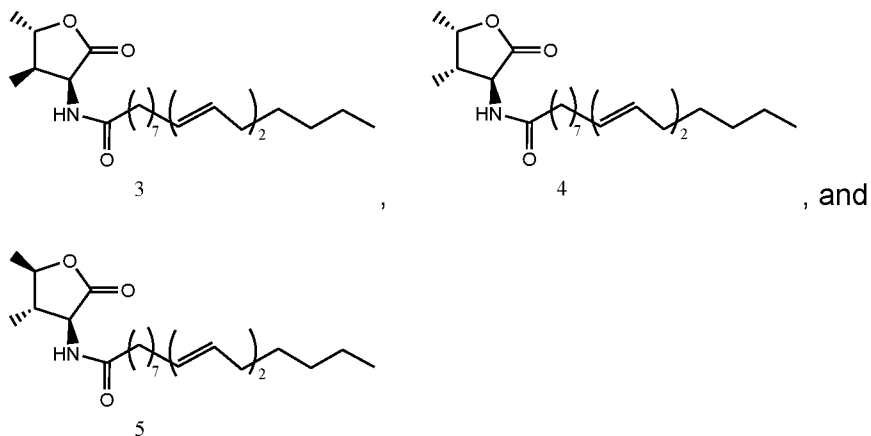
[0051] The present invention thus further encompasses stereoisomeric mixtures of compounds disclosed herein. It also encompasses configurational isomers of compounds disclosed herein (e.g., cis and trans isomers, whether or not involving double bonds), either in admixture or in pure or substantially pure form.

[0052] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-1),

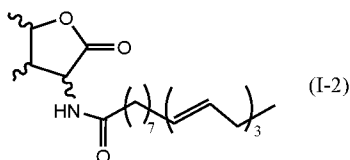


[0053] Exemplary compounds of formula (I-1) described herein include, but are not limited to,

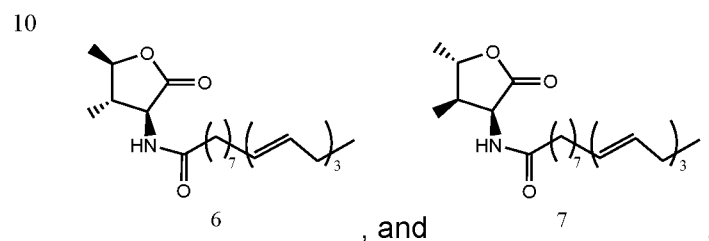




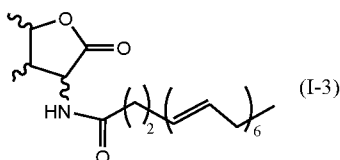
[0054] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-2),



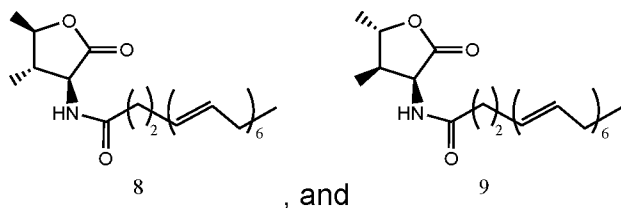
[0055] Exemplary compounds of formula (I-2) described herein include, but are not limited to,



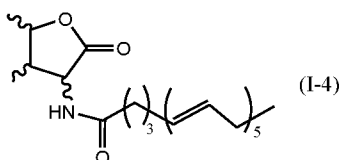
[0056] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-3),



[0057] Exemplary compounds of formula (I-3) described herein include, but are not limited to,

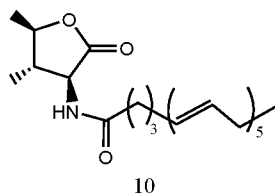


[0058] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-4),

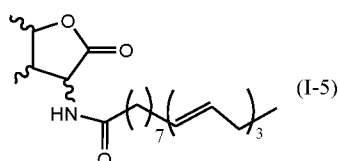


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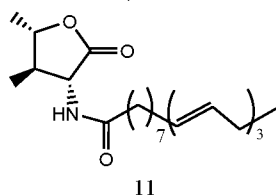
[0059] Exemplary compound of formula (I-4) described herein includes, but is not limited to,



[0060] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-5),

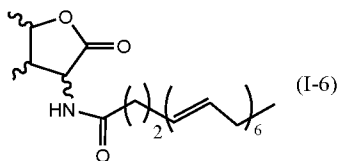


[0061] Exemplary compound of formula (I-5) described herein includes, but is not limited to,

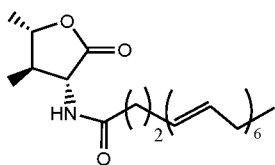


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[0062] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-6),

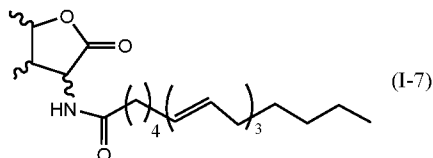


[0063] Exemplary compound of formula (I-6) described herein includes, but is not limited to,

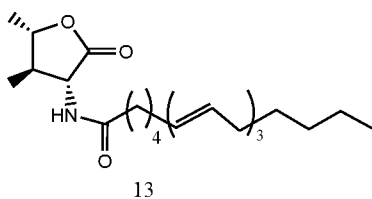


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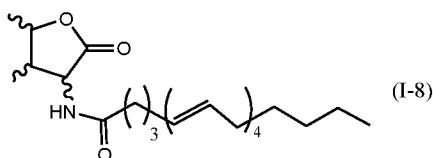
[0064] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-7),



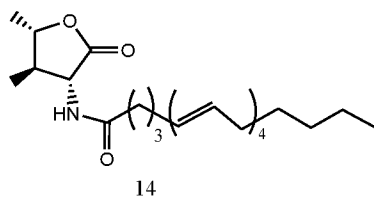
10 [0065] Exemplary compound of formula (I-7) described herein includes, but is not limited to,



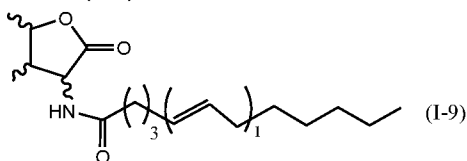
15 [0066] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-8),



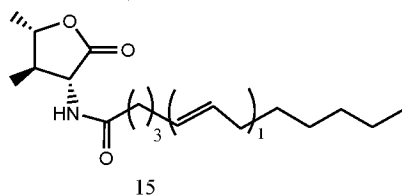
[0067] Exemplary compound of formula (I-8) described herein includes, but is not limited to,



[0068] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-9),

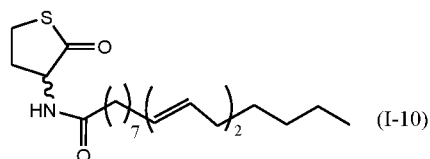


5 [0069] Exemplary compound of formula (I-9) described herein includes, but is not limited to,

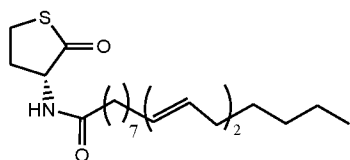


[0070] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-10),

10

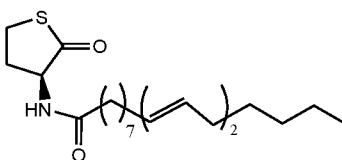


[0071] Exemplary compounds of formula (I-10) described herein include, but are not limited to,

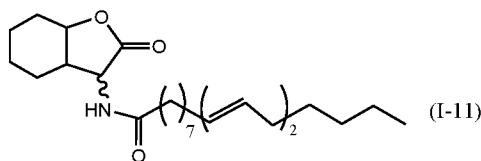


15

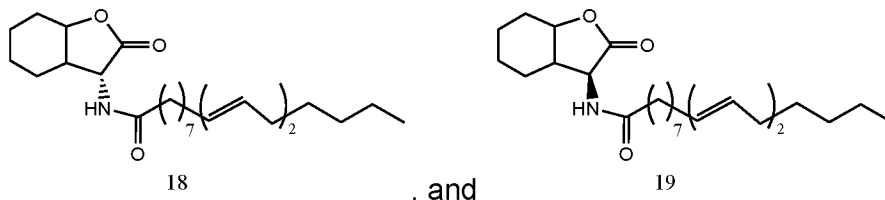
, and



[0072] According to certain embodiments, particular compounds of formula (I) has the structure of formula (I-11),



[0073] Exemplary compounds of formula (I-10) described herein include, but are not limited to,



5 [0074] 3. Method of Use

[0075] The present invention encompasses a method for the treatment or prophylaxis of a subject having or suspected of having a disease and/or disorder associated with hyperglycemia. The method comprises the step of administering a therapeutically or prophylactically effective amount of the compound of formula (I) of the present disclosure to the subject, so as to reduce the blood sugar level of the subject, thereby ameliorates, mitigates and/or prevents the symptoms of the disease and/or disorder associated with hyperglycemia.

[0076] In some embodiments, the method further includes the step of administering to the subject a blood sugar reducing agent, before, together with, or after the administration of the compound of formula (I). The blood sugar reducing agent may be selected from the group consisting of, alpha-glucosidase inhibitor, biguanide, dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor, sulfonylurea, and thiazolidinedione.

[0077] According to embodiments of the present disclosure, the alpha-glucosidase inhibitor is acarbose or miglitol. Suitable example of the biguanide is metformin. Suitable example of the dopamine agonist is bromocriptine. Suitable examples of the DPP-4 inhibitor include, but are not limited to, alogliptin, linagliptin, saxagliptin, sitagliptin, and simvastatin. Suitable examples of the GLP-1 include, but are not limited to, lixisenatide, albiglutide,

dulaglutide, exenatide, and liraglutide. Suitable examples of the SGLT 2 inhibitor include, but are not limited to, dapagliflozin, canagliflozin, and empagliflozin. Suitable examples of the sulfonylurea include, but are not limited to, glimepiride, gliclazide, glipizide, glyburide, chlorpropamide, tolazamide, and tolbutamide. Suitable examples of the thiazolidinedione include, but are not limited to, pioglitazone and rosiglitazone.

[0078] In the present disclosure, the diseases and/or disorders associated with hyperglycemia may be diabetes, obesity, impaired glucose tolerance, impaired fasting glycemia (IFG), hyperinsulinemia, hyperlipidemia, hyper-cholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia, gout, diabetic complication and the like.

[0079] According to some embodiments of the present disclosure, the diseases and/or disorders associated with hyperglycemia is diabetes, which includes, but is not limited to, type 1 or 2 diabetes, and gestational diabetes. According to one preferred embodiment, the diseases and/or disorders associated with hyperglycemia treatable by the present method is type 2 diabetes.

[0080] According to other embodiments of the present disclosure, the diseases and/or disorders associated with hyperglycemia is the diabetic complication, which may be retinopathy, neuropathy, nephropathy, ulcer, or macroangiopathy.

[0081] The amount, route of administration and dosing schedule of the compound of formula (I) will depend upon factors such as the specific indication to be treated, prevented, or managed, and the age, sex and condition of the patient. The roles played by such factors are well known in the art, and may be accommodated by routine experimentation.

[0082] 4. Pharmaceutical Formulation

[0083] This invention encompasses pharmaceutical compositions for the treatment or prophylaxis of a disease and/or disorder associated with hyperglycemia. The pharmaceutical composition comprises a therapeutically or prophylactic effective amount of a compound of formula (I) of the present invention.

[0084] The compound of formula (I) is present at a level of about 0.1% to 99% by weight, based on the total weight of the pharmaceutical composition. In some embodiments, the compound of formula (I) is present at a level of at least 1% by weight, based on the total weight of the pharmaceutical composition. In
5 certain embodiments, the compound of formula (I) is present at a level of at least 5% by weight, based on the total weight of the pharmaceutical composition. In still other embodiments, the compound of formula (I) is present at a level of at least 10% by weight, based on the total weight of the pharmaceutical composition. In still yet other embodiments, the compound of formula (I) is
10 present at a level of at least 25% by weight, based on the total weight of the pharmaceutical composition.

[0085] In some preferred embodiments, the pharmaceutical composition further comprises a blood sugar reducing agent. The blood sugar reducing agent may be selected from the group consisting of, alpha-glucosidase inhibitor, biguanide,
15 dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor, sulfonylurea, and thiazolidinedione.

[0086] According to one embodiment of the present disclosure, the pharmaceutical composition further comprises the alpha-glucosidase inhibitor,
20 which may be acarbose or miglitol.

[0087] According to another embodiment of the present disclosure, the pharmaceutical composition further comprises the biguanide, which preferably is metformin.

[0088] According to still another embodiment of the present disclosure, the
25 pharmaceutical composition further comprises the dopamine agonist, which may be bromocriptine.

[0089] According to a further embodiment of the present disclosure, the pharmaceutical composition further comprises the DPP-4 inhibitor, and examples of the DPP-4 inhibitor include, but are not limited to, alogliptin,
30 linagliptin, saxagliptin, sitagliptin, and simvastatin.

[0090] According to other embodiment of the present disclosure, the pharmaceutical composition further comprises GLP-1. Suitable examples of GLP-1 include, but are not limited to, lixisenatide, albiglutide, dulaglutide, exenatide, and liraglutide.

5 [0091] According to yet another embodiment of the present disclosure, the pharmaceutical composition further comprises SGLT 2 inhibitor. Suitable examples of the SGLT 2 inhibitor include, but are not limited to, dapagliflozin, canagliflozin, and empagliflozin.

[0092] According to further embodiment of the present disclosure, the
10 pharmaceutical composition further comprises the sulfonylurea. Suitable examples of the sulfonylurea include, but are not limited to, glimepiride, gliclazide, glipizide, glyburide, chlorpropamide, tolazamide, and tolbutamide.

[0093] According to still further embodiment of the present disclosure, the pharmaceutical composition further comprises thiazolidinedione, which may be
15 pioglitazone or rosiglitazone.

[0094] Certain pharmaceutical compositions are single unit dosage forms suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intra-arterial), or transdermal administration to a patient. Examples of dosage
20 forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including
25 suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

30 [0095] The formulation should suit the mode of administration. For example, oral administration requires enteric coatings to protect the compounds of this

invention from degradation within the gastrointestinal tract. Similarly, a formulation may contain ingredients that facilitate delivery of the active ingredient(s) to the site of action. For example, compounds may be administered in liposomal formulations, in order to protect them from degradative enzymes, facilitate transport in circulatory system, and effect delivery across cell membranes to intracellular sites.

[0096] Similarly, poorly soluble compounds may be incorporated into liquid dosage forms (and dosage forms suitable for reconstitution) with the aid of solubilizing agents, emulsifiers and surfactants such as, but not limited to, cyclodextrins (*e.g.*, α -cyclodextrin or β -cyclodextrin), and non-aqueous solvents, such as, but not limited to, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, dimethyl sulfoxide (DMSO), biocompatible oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, and mixtures thereof (*e.g.*, DMSO:corn oil).

[0097] The composition, shape, and type of a dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[0098] 4.1 Oral Dosage Forms

[0099] Pharmaceutical compositions of the present invention suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active

ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[00100] Typical oral dosage forms are prepared by combining the active
5 ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration.

[00101] Because of their ease of administration, tablets and capsules represent
10 the most advantageous oral dosage unit forms. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by conventional methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid
15 carriers, or both, and then shaping the product into the desired presentation if necessary. Dis-integrants may be incorporated in solid dosage forms to facilitate rapid dissolution. Lubricants may also be incorporated to facilitate the manufacture of dosage forms (e.g., tablets).

[00102] **4.2 Parenteral Dosage Forms**

20 [00103] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are specifically sterile or capable of being sterilized prior to
25 administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[00104] Suitable vehicles that can be used to provide parenteral dosage forms of
30 the invention are well known to those skilled in the art. Examples include, but are not limited to: water; aqueous vehicles such as, but not limited to, sodium

chloride solution, Ringer's solution, and Dextrose; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5 [00105] **4.3 Transdermal, Topical and Mucosal Dosage Forms**

[00106] Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th eds., Mack
10 Publishing, Easton PA (1990). Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[00107] Suitable excipients (*e.g.*, carriers and diluents) and other materials that
15 can be used to provide transdermal, topical, and mucosal dosage forms are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied.

[00108] Depending on the specific tissue to be treated, additional components
20 may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers may be used to assist in delivering active ingredients to the tissue.

[00109] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be
25 adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates may also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve
30 delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing

or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition

[00110] **5. Kits**

5 [00111] Also encompasses within the present disclosure are kits useful for treatment or prophylaxis of a disease and/or disorder associated with hyperglycemia in a subject.

[00112] The Kit according to present disclosure include, at least, a first container containing a blood sugar reducing agent, a second container
10 containing the present compound of formula (I); and a legend associated with the kit for instructing a user how to use the kit. The legend may be in a form of pamphlet, tape, CD, VCD or DVD. Examples of the container include, but are not limited to, vials, tubes, and the like.

[00113] The present invention will now be described more specifically with
15 reference to the following embodiments, which are provided for the purpose of demonstration rather than limitation. While they are typically of those that might be used, other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

20

EXAMPLES

[00114] **Materials and Methods**

[00115] *Cell culture*

[00116] The *RINm5F* cells and H460 were grown in manufactures' suggested medium supplemented with 10% heat-inactivated fetal bovine serum, 100
25 units/mL penicillin, and 100 µg/mL streptomycin, at 37 °C in a humidified 5% CO₂ incubator.

[00117] *cAMP assay*

[00118] Real time intracellular cAMP assay was performed as described previously (Cheng et al., J. Biol Chem. 290, 14302-14313 (2015)). Briefly,
30 *RINm5F* cells stably expressing the RG-cAMP protein were seeded at a density

of 3×10^4 cells/well in 96-well plates in 0.15 ml of RPMI 1640 medium containing 400 µg/ml G418. Next day, cells were washed twice with 0.1 ml phenol red-free MEM containing 5 mM HEPES, and incubated in the same medium for 1 h. The medium was replaced with 90 µL the same medium containing 1 mg/ml BSA and 5 µM DeepBlueC. The whole plate was immediately loaded onto a SpectraMax Paradigm Detection Platform equipped with a Dual-Color luminescence detection cartridge and SoftMax Pro 6.2.2 (Molecular Devices, Sunnyvale, CA) to obtain the background BRET signal based on the sequential integration of the luminescence detected at 370–450 and 500–530 nm over 60–150 s. Each well was then stimulated by adding 10 µl of 10x solutions of peptide and lipids and 1 mg/ml BSA in phenol red-free MEM containing 5 mM HEPES, and BRET signals were obtained immediately under identical settings. The BRET ratio is the ratio of light emitted between 90 and 300 s at 500–530 nm to that emitted at 370–450 nm. The cAMP response was expressed as a percentage of cAMP production, and was calculated as $100 \times (\text{BRET ratio from 0.01 GLP-1(7-36)-amide} - \text{BRET ratio from indicated concentration of peptide with or without lipids}) / (\text{BRET ratio from 0.01 nM GLP-1(7-36)-amide} - \text{BRET ratio from 250 nM GLP-1(7-36)-amide})$. The dose-response curve, maximal response, and concentration of peptide needed to yield half-maximal response (EC₅₀) were obtained by nonlinear regression to fit the data to the agonist *versus* response equation using Prism software 5.0 (GraphPad, San Diego). Unless specified, all cAMP response data are the means $\pm$ S.E. from three independent experiments with triplicate assays.

[00119] *Receptor endocytosis assay.*

[00120] U2OS osteosarcoma cell line stably expressing a β -arrestin2:GFP fusion protein was obtained from Norak Biosciences. The pcDNA3 GLP-1R-V2R chimeric construct contains the first 440 amino acids of the GLP-1R (Met-1 to Thr-440) fused to the last 29 amino acids of the vasopressin V2 receptor (Ala-343 to Ser-371) and separated by two alanine residues as

linker. GLP-1R-V2R chimeric construct was inserted into the EcoRI site of pcDNA3 (pcDNA3-GLP-1R-V2R) such that expression of the chimeric protein was under the control of the CMV promoter. pcDNA3-GLP-1R-V2R was used to transfect U2OS osteosarcoma cells stably expressing β -arrestin2:GFP to obtain a cell line stably co-expressing GLP-1R-V2R and β -arrestin2:GFP. High content imaging of receptor endocytosis in cells was conducted with 0.03 to 0.001 mg/ml of the test compound to identify potentiating activity for GLP-1-dependent GLP-1R endocytosis. Three replicate 384-well assay microplates were plated with U2OS cells stably co-expressing GLP-1R-V2R and β -arrestin2: GFP at a density of 3×10^3 cells/well. Aliquots of 2.5 μ l of 10X stocks of the indicated concentration of the test compound in phenol red-free MEM containing increasing concentrations (0.12 to 3,000 nM) of GLP-1(7–36)-amide and 1 mg/ml BSA were transferred to each well of the assay plate, which contained 22.5 μ l of phenol red-free MEM containing 1 mg/ml BSA. The three assay plates were incubated at room temperature for 60 min before cell fixation with 2% formaldehyde and labeling of the cell nuclei with 5 μ g/ml of the DNA-binding dye Hoechst 33342 for 1 h. Plates were washed twice with PBS and sealed; plates were used immediately.

[00121] *Image and analysis*

[00122] Images were acquired on an XL model of the ImageXpress® Micro System (Molecular Devices, Sunnyvale, CA) and analyzed with MetaXpress High-Content Image Acquisition and Analysis Software (Molecular Devices, Sunnyvale, CA) using the granularity and variable grain analysis modules. MetaXpress was used to retrieve images using DAPI (to retrieve the blue fluorescent Hoechst 33342-labeled nuclear images) and FITC (to retrieve the green fluorescent GFP- β -arrestin images) filter sets and a Plan Fluor ELWD objective. A 20 x0.45-numerical aperture microscope objective was used for the imaging, two fields were imaged per well. The number of spots, total area covered by spots, average and integrated fluorescence intensity of the spots,

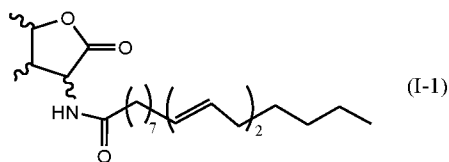
and nuclear area and fluorescence intensity were logged into the database. Data from abnormal cells for which the values were above threshold (abnormal: average nuclear staining intensity <500; integrated fluorescence intensity of area covered by spots <150) were ruled out using Acuity Xpress, followed by
5 selection of the measurement method, spot fluorescence integrated intensity to calculate the average number of spots per nucleus. Dose-response curve, maximal response, and the concentration needed to yield half-maximal response were obtained using nonlinear regression to fit the data to the agonist *versus* response equation with Prism software 5.0. The extent of receptor endocytosis
10 response was expressed as percent of that elicited by 750 MGLP-1(7–36)-amide.

[00123] *Cell Viability Test*

[00124] Cytotoxicity of H460 cells to various compounds was assessed using PrestoBlue® reagent, which was modified by the reducing environment of the
15 viable cell and turns from blue to red in color. In brief, 3,000 H460 cells were seeded with 0.1 ml of RPMI 1640 medium in each well of a 96-well plate and incubated at 37 °C for 24 h before compound treatment. After a 72-h compound treatment, PrestoBlue™ cell viability reagent (Invitrogen) was added to each well according to the manufacturer's protocol. The plates were further
20 incubated in the dark at 37 °C in 5% CO₂ for 10 min, and absorbance of all wells was read at both the 570- and 600-nm wavelengths using automatic enzyme-linked immunosorbent assay plate reader (Molecular Devices, Union City, CA). The raw data were normalized and corrected according to the manufacturer's protocol. All samples were tested in triplicate, and each test was
25 repeated three times. Cell viability was calculated using the following formula: percent of 100 x (average corrected values of compound treated cells)/(average corrected values of untreated cells).

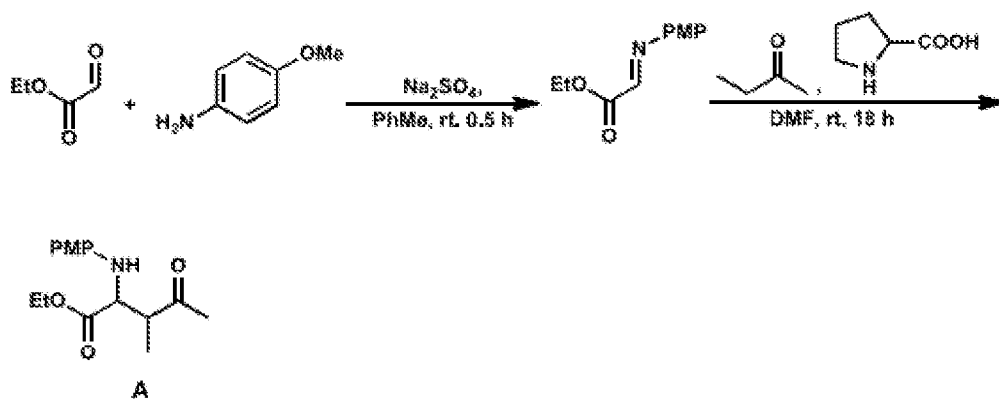
[00125] **EXAMPLE 1 Preparation of Exemplary Compounds of Formula (I)**

[00126] 1.1 Synthesis of compounds of formula (I-1)



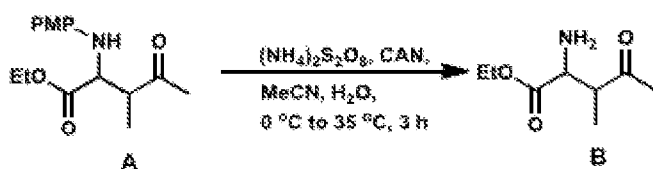
[00127] Step 1:

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[00128] **Ethyl 2-(4-Methoxyphenylamino)-3-methyl-4-oxopentanoate (A):**

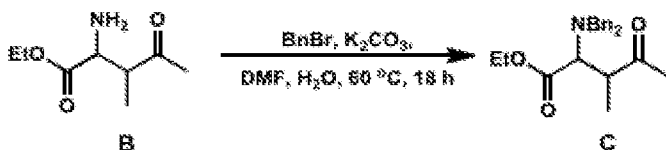
Na₂SO₄ (10.7 g, 75.0 mmol) was added to a stirred solution of 4-anisidine (3.69 g, 30.0 mmol) in toluene (PhMe) (30.0 mL), followed by the addition of ethyl glyoxalate (6.13 mL, 30.0 mmol, 50% in toluene) within 10 to 20 min. The reaction mixture was stirred at room temperature for 30 min. After the starting material was consumed, Na₂SO₄ was filtered out by Celite, and the filtrate was concentrated under reduced pressure to give a brown oil that was used immediately for the next step without further purification. A solution of the brown oil in dry dimethylformamide (DMF) (15.5 mL) was slowly added to a stirred solution of butanone (59.0 mL, 660 mmol) and proline (1.21 g, 10.5 mmol) in dry DMF (46.6 mL) over 30 min at room temperature, and the resulting mixture was stirred at room temperature for 12 h. After the starting material was consumed, the reaction mixture was filtered through a pad of sieve and concentrated under reduced pressure. The resulting yellow oil was directly used for the next reaction without further purification. A small amount of mixture was applied to column chromatography (silica gel, EtOAc/hexane = 1/4) and then HPLC for the characterization of the compound (A). R_f = 0.25 (EtOAc/hexane = 1/5, UV); IR

(film) $\nu = 3379, 2981, 2936, 1729, 1713, 1514, 1235, 1200, 1180, 1035, 823 \text{ cm}^{-1}$;
 ^1H NMR (400 MHz, CDCl_3) δ 6.77 (d, $J = 8.8 \text{ Hz}$, 2 H), 6.66 (d, $J = 8.8 \text{ Hz}$, 2 H),
 4.31 (d, $J = 5.8 \text{ Hz}$, 1 H), 4.19–4.13 (m, 2 H), 3.74 (s, 3 H), 3.03 (m, 1 H), 2.23 (s,
 3 H), 1.25 (d, $J = 7.1 \text{ Hz}$, 3 H), 1.22 (t, $J = 7.2 \text{ Hz}$, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ
 209.3, 172.9, 153.3, 140.9, 116.0, 115.0, 61.5, 59.8, 55.8, 49.4, 28.6, 14.3, 12.4.
 [00129] Step 2:



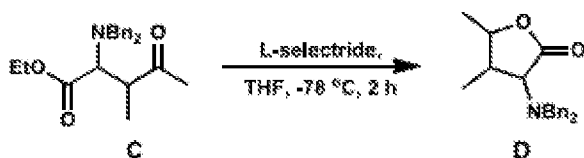
[00130] **Ethyl -2-Amino-3-methyl-4-oxopentanoate (B):** A solution of
 10 $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (913 mg, 4.0 mmol) and cerium ammonium nitrate (CAN) (110 mg,
 0.2 mmol) in H_2O (5.8 mL) was slowly added to a stirred solution of the mixture
 from Step 1, the compound (A) (547 mg, 2.0 mmol) in acetonitrile (MeCN) (1.0 mL)
 at 0°C . The resulting mixture was then heated to 35°C and stirred for 3 h. Upon
 the completion of the reaction, the reaction mixture was diluted with H_2O (5.8 mL)
 15 and washed with CH_2Cl_2 (5 mL $\times$ 4). The aqueous layer was basified with 1 M
 Na_2CO_3 aqueous solution to pH ~ 8 and then extracted with CH_2Cl_2 (15 mL $\times$ 5).
 The combined organic layers were dried over Na_2SO_4 and concentrated under
 reduced pressure to give a brown liquid that contains the compound (B) (229 mg).
 The crude mixture was used immediately for the next reaction without further
 20 purification. Characterization of the compound (B): $R_f = 0.40$ (methanol/ $\text{CH}_2\text{Cl}_2 =$
 $1/10$, ninhydrin); ^1H NMR (400 MHz, CDCl_3) δ 4.19–4.13 (m, 2 H), 3.86 (d, $J = 4.8$
 Hz, 1 H), 2.91 (m, 1 H), 2.19 (s, 3 H), 1.25 (t, $J = 7.1 \text{ Hz}$, 3 H), 1.11 (d, $J = 7.2 \text{ Hz}$,
 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.9, 174.3, 61.3, 55.4, 49.8, 28.4, 14.2,
 11.0; HRMS (APCI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_8\text{H}_{16}\text{O}_3\text{N}$ 174.1130, found
 25 174.1127.

[00131] Step 3:



[00132] **Ethyl 2-(Dibenzylamino)-3-methyl-4-oxopentanoate (C):** A suspension of the crude mixture from Step 2, the compound (B) (98 mg, 0.57 mmol) and K_2CO_3 (235 mg, 1.7 mmol) in DMF/ H_2O (1.1 mL/0.11 mL) was stirred at room temperature for 15 min, followed by the dropwise addition of benzyl bromide (BnBr) (0.34 mL, 2.8 mmol). After stirring at 60 °C for 18 h, H_2O (5 mL) was added, and the reaction mixture was then extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/15) to give the compound (C) as a white solid (120 mg, 0.34 mmol, 60%). R_f = 0.45 (EtOAc/hexane = 1/5, UV); mp 58.8–62.3 °C; IR (film) ν = 3062, 3029, 2977, 2929, 2852, 1723, 1602, 1495, 1454, 1370, 1201, 1169, 1026, 961, 748, 699 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10 H), 4.34–4.16 (m, 2 H), 3.86 (d, J = 13.5 Hz, 2 H), 3.49 (d, J = 10.9 Hz, 1 H), 3.45 (d, J = 13.4 Hz, 2 H), 3.08 (dt, J = 10.9, 7.2 Hz, 1 H), 2.15 (s, 3 H), 1.38 (t, J = 7.1 Hz, 3 H), 1.10 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 171.9, 138.9, 129.2, 128.4, 127.3, 62.6, 60.5, 55.2, 46.0, 29.2, 14.7, 14.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{22}H_{28}O_3N_2$ 354.2069, found 354.2061.

[00133] Step 4:

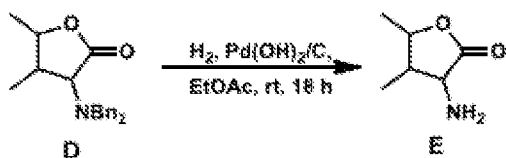


[00134] **3-(Dibenzylamino)-4,5-dimethyldihydrofuran-2(3H)-one (D):** L-selectride [0.54 mL, 1.0 M in tetrahydrofuran (THF), 0.54 mmol] was added to a stirred solution of the compound (C) (173 mg, 0.49 mmol) in dry THF (4.9 mL) at –78 °C under nitrogen. After stirring for 2 h at –78 °C, the reaction mixture was poured into a vigorously stirred mixture of EtOAc/1 M HCl aqueous solution (10.0

mL/10.0 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with H₂O (5 mL × 3–5) until pH ~ 6 and then washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel
 5 (EtOAc/hexane = 1/20, UV) to give the compound (D) as a white solid (143 mg, 0.46 mmol, 94%). R_f = 0.33 (EtOAc/hexane = 1/10, UV); mp 66.5–69.7 °C; IR (film) ν = 3062, 3028, 2972, 2928, 2850, 1769, 1601, 1493, 1454, 1385, 1325, 1236, 1185, 1171, 1141, 1050, 995, 953, 745, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.40 (m, 4 H), 7.35–7.31 (m, 4 H), 7.28–7.23 (m, 2 H), 4.00 (d, J =
 10 13.8 Hz, 2 H), 3.91–3.83 (m, 3 H), 3.29 (d, J = 11.8 Hz, 1 H), 2.05 (m, 1 H), 1.35 (d, J = 6.1 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 175.3, 139.4, 128.8, 128.4, 127.3, 79.6, 65.4, 54.9, 42.1, 18.9, 14.1; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd. for C₂₀H₂₃O₂NNa 332.1626, found 332.1623.

[00135] Step 5:

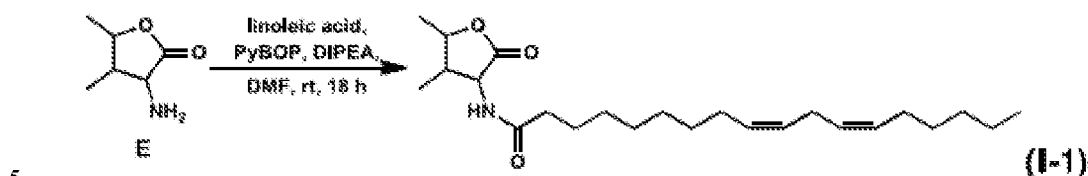
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[00136] **3-Amino-4,5-dimethyldihydrofuran-2(3H)-one (E)**: Pd(OH)₂/C (6.2 mg, 20%) was added to a stirred solution of the compound (D) (61.9 mg, 0.20 mmol) in EtOAc (4.0 mL) under nitrogen and then purged with hydrogen (1 atm, balloon) for an hour at room temperature. After stirring at room temperature under hydrogen for 18 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to give the compound (E) as a colorless oil (25.8 mg, 0.20 mmol, >99%) without further purification. R_f = 0.4 (methanol/CH₂Cl₂ = 1/10, ninhydrin); IR (film) ν = 3374, 3310, 2973, 2927, 2878,
 20 2852, 1771, 1456, 1389, 1330, 1192, 1145, 1044, 983, 946, 918, 735, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.05 (dq, J = 9.9, 6.1 Hz, 1 H), 3.25 (d, J = 5.2 Hz, 1 H), 1.80 (m, 1 H), 1.73 (s, 2 H), 1.42 (d, J = 6.2 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H);
 25

^{13}C NMR (100 MHz, CDCl_3) δ 178.2, 79.8, 58.9, 47.5, 18.6, 14.2; HRMS (EI+) m/z $M + \text{calcd. for } \text{C}_6\text{H}_{11}\text{O}_2\text{N}$ 129.0790, found 129.0791.

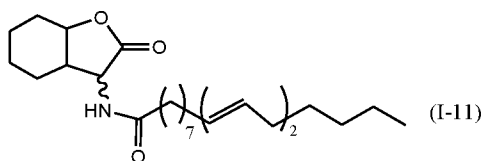
[00137] Step 6:



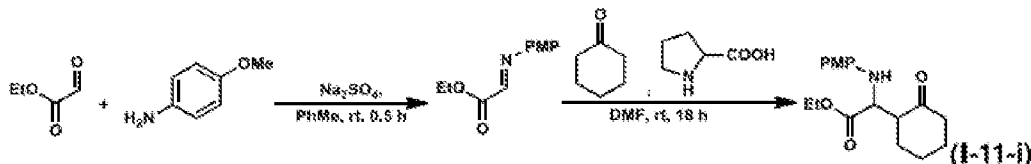
[00138] **(9Z,12Z)-N-(4,5-Dimethyl-2-oxotetrahydrofuran-3-yl)octadeca-9,12-dienamide (I-1):** Benzotriazol-1-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (62.5 mg, 0.12 mmol) was added to a stirred solution of the compound (E) (12.9 mg, 0.10 mmol) and linoleic acid (31 μL , 0.10 mmol) in dry DMF (1.0 mL), followed by freshly distilled N,N-diisopropylethylamine (DIPEA) (21 μL , 0.12 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 18 h. After the starting material was consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4) to give the compound (I-1) as a colorless oil (36.9 mg, 0.094 mmol, 94%). R_f = 0.28 [ethyl acetate (EtOAc)/hexane = 1/2, I2]; IR (film) ν = 3303, 3009, 2957, 2927, 2855, 1782, 1657, 1650, 1533, 1461, 1454, 1389, 1187, 1047, 908, 723 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 5.39–5.29 (m, 4 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.19 (dt, J = 9.8, 6.1 Hz, 1H), 2.78 (t, J = 6.5 Hz, 2 H), 2.26 (t, J = 7.5 Hz, 2 H), 2.17–2.04 (m, 5 H), 1.66–1.60 (m, 2 H), 1.41 (d, J = 6.1 Hz, 3 H), 1.40–1.28 (m, 14 H), 1.13 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.5, 176.2, 130.9, 130.9, 129.1, 129.1, 81.4, 57.5, 45.6, 36.9, 32.7, 30.7, 30.5, 30.3, 30.3, 30.2, 28.2, 26.8, 26.5, 23.6, 18.8, 14.4, 14.0; HRMS (MALDI-TOF) m/z [$M + \text{Na}$] $^+$ calcd. for $\text{C}_{24}\text{H}_{41}\text{O}_3\text{NNa}$ 414.2979, found 414.2963.

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[00139] **1.2 Synthesis of compound of formula (I-11)**

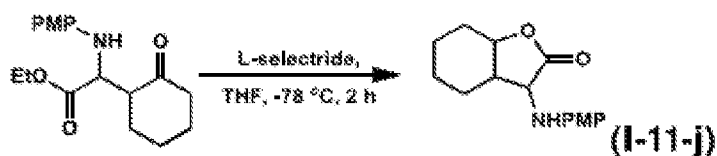


[00140] Step 1:



- [00141] **Ethyl 2-(4-Methoxyphenylamino)-2-(2'-oxocyclohex-1'-yl)acetate (I-11-i)**: Na₂SO₄ (1.77 g, 12.5 mmol) was added to a stirred solution of 4-anisidine (616 mg, 5.0 mmol) in toluene (PhMe) (5.0 mL), followed by the addition of ethyl glyoxalate (1.02 mL, 5.0 mmol, 50% in toluene) within 10 to 20 min. The reaction mixture was stirred at room temperature for 30 min. After the starting material was consumed, Na₂SO₄ was filtered out by Celite, and the filtrate was concentrated under reduced pressure to give a brown oil that was used immediately for the next step without further purification. A solution of the brown oil in dry dimethylformamide (DMF) (2.6 mL) was slowly added to a stirred solution of cyclohexanone (8.4 mL, 110 mmol) and proline (201 mg, 1.75 mmol) in dry DMF (7.8 mL) over 30 min at room temperature, and the resulting mixture was stirred at room temperature for 12 h. After the starting material was consumed, the reaction mixture was filtered through a pad of sieve and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/5) to give the compound (I-11-i) as an orange solid (1.24 g, mmol, 81%). R_f = 0.45 (EtOAc/hexane = 1/2, UV); ¹H NMR (400 MHz, CDCl₃) δ 6.78–6.71 (m, 4 H), 4.23 (d, J = 4.9 Hz, 1 H), 4.19–4.10 (m, 2 H), 3.90 (br-s, 1 H), 3.73 (s, 3 H), 2.80 (m, 1 H), 2.48–2.44 (m, 1 H), 2.35–2.26 (m, 1 H), 2.22–2.04 (m, 1 H), 1.96–1.93 (m, 1 H), 1.86–1.67 (m, 4 H), 1.21 (t, J = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 210.1, 173.5, 153.2, 141.3, 116.2, 114.9, 61.2, 58.2, 55.8, 53.7, 41.9, 29.7, 26.9, 24.9, 14.2.

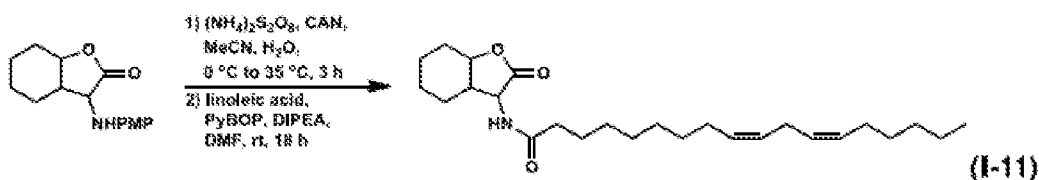
[00142] Step 2:



[00143] **3-(4-Methoxyphenylamino)hexahydrobenzofuran-2(3H)-one (I-11-j):**

L-selectride [0.55 mL, 1.0 M in tetrahydrofuran (THF), 0.55 mmol] was added to a stirred solution of the compound (I-11-i) (153 mg, 0.50 mmol) in dry THF (5.0 mL) at $-78\text{ }^{\circ}\text{C}$ under nitrogen. After stirring for 2 h at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was poured into a vigorously stirred mixture of EtOAc/1 M HCl aqueous solution (10.0 mL/10.0 mL). The aqueous layer was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with H_2O (5 mL $\times$ 3–5) until pH $\sim$ 6 and then washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4, UV) to give the compound (I-11-j) as a yellow oil (87 mg, 0.33 mmol, 67%). R_f = 0.43 (EtOAc/hexane = 1/2, UV); ^1H NMR (400 MHz, CDCl_3) δ 6.78 (d, J = 8.8 Hz, 2 H), 6.68 (d, J = 8.9 Hz, 2 H), 4.59 (m, 1 H), 3.96 (d, J = 8.4 Hz, 1 H), 3.74 (s, 3 H), 2.44 (m, 1 H), 2.04–1.94 (m, 1 H), 1.77–1.60 (m, 4 H), 1.55–1.48 (m, 2 H), 1.40–1.30 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.7, 153.3, 140.9, 115.6, 115.0, 77.0, 57.9, 55.8, 41.8, 29.0, 24.6, 21.5, 21.4.

[00144] Step 3:

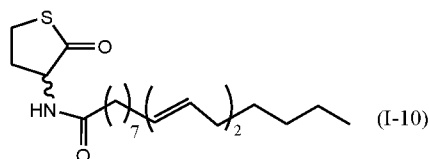


[00145] **(9Z,12Z)-N-(2-Oxo-octahydrobenzofuran-3-yl)octadeca-9,12-dienamide (I-11):**

A solution of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (69.9 mg, 0.31 mmol) and cerium ammonium nitrate (CAN) (8.4 mg, 0.015 mmol) in H_2O (0.77 mL) was slowly added to a stirred solution of the compound (I-11-j) (40.0 mg, 0.15 mmol) in acetonitrile (MeCN) (0.6 mL) at $0\text{ }^{\circ}\text{C}$. The resulting mixture was then heated to $35\text{ }^{\circ}\text{C}$ and stirred for 3 h. Upon the completion of the reaction, the reaction mixture was diluted with H_2O (2 mL) and washed with CH_2Cl_2 (2 mL $\times$ 4). The aqueous

layer was basified with 1 M Na₂CO₃ aqueous solution to pH ~ 8 and then extracted with CH₂Cl₂ (5 mL × 5). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give a crude as a brown liquid (13.1 mg, ~0.084 mmol, ~55%). PyBOP (52.7 mg, 0.10 mmol) was added to a stirred solution of the crude (13.1 mg, ~0.084 mmol) and linoleic acid (26 μL, 0.084 mmol) in dry DMF (0.84 mL), followed by freshly distilled N,N-diisopropylethylamine (DIPEA) (18 μL, 0.10 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 18 h. After the starting material was consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with H₂O (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4) to give the compound (I-11) as a colorless oil (29.3 mg, 0.070 mmol, 83%). R_f = 0.4 (EtOAc/hexane = 1/2, I2); IR (film) ν = 3296, 3009, 2927, 2855, 1785, 1657, 1650, 1547, 1536, 1463, 1453, 1175, 1126, 1015, 725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.01 (d, J = 8.0 Hz, 1 H), 5.40–5.29 (m, 4 H), 4.92 (dd, J = 8.1, 12.3 Hz, 1 H), 4.51 (dt, J = 10.7, 6.7 Hz, 1 H), 2.76 (t, J = 6.7 Hz, 2 H), 2.48–2.43 (m, 1 H), 2.29–2.21 (m, 2 H), 2.21–2.17 (m, 1 H), 2.06–2.01 (m, 4 H), 1.92–1.89 (m, 1 H), 1.81–1.78 (m, 1 H), 1.71–1.52 (m, 5 H), 1.44–1.19 (m, 16 H), 0.88 (t, J = 6.8 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 175.9, 174.1, 130.3, 130.1, 128.1, 128.0, 77.3, 49.7, 42.3, 36.4, 31.6, 29.7, 29.4, 29.4, 29.3, 29.2, 27.3, 25.7, 25.5, 24.2, 22.7, 22.5, 20.0; HRMS (MALDI-TOF) m/z [M + Na]⁺ calcd. for C₂₆H₄₃O₃NNa 440.3135, found 440.3145.

[00146] 1.3 Synthesis of exemplary compound of formula (I-10)



[00147] PyBOP (122 mg, 0.23 mmol) was added to a stirred solution of the starting material (I-10-i) (30.0 mg, 0.20 mmol), linoleic acid (61 μL, 0.20 mmol), and freshly distilled DIPEA (75 μL, 0.43 mmol) in dry DMF (2.0 mL) at room

temperature under nitrogen. The reaction mixture was stirred for 18 h. After the starting material was consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with H₂O (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/2) to give the compound (I-10) as a colorless solid (71.0 mg, 0.19 mmol, 96%). R_f = 0.45 (EtOAc/hexane = 1/1, I₂); IR (film) ν = 3283, 3008, 2926, 2854, 1711, 1650, 1536, 1462, 1275, 1055, 1019, 916, 724 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.90 (d, J = 4.7 Hz, 1 H), 5.41–5.29 (m, 4 H), 4.50 (m, 1 H), 3.36 (dt, J = 5.1, 11.8 Hz, 1 H), 3.25 (dd, J = 6.8, 11.3 Hz, 1 H), 2.97 (m, 1 H), 2.76 (t, J = 6.6 Hz, 2 H), 2.23 (dt, J = 2.3, 7.6 Hz, 2 H), 2.04 (m, 4 H), 1.90 (m, 1 H), 1.65–1.60 (m, 2 H), 1.38–1.25 (m, 14 H), 0.88 (t, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.8, 173.8, 130.3, 130.1, 128.2, 128.0, 59.6, 36.5, 32.3, 31.6, 29.7, 29.4, 29.3, 29.3, 29.2, 27.7, 27.3, 25.7, 25.6, 22.7, 14.2; HRMS (MALDI-TOF) m/z [M + H]⁺ calcd. for C₂₂H₃₈O₂NS 380.2614, found 380.2614.

[00148] **Example 2 Compounds of Formula (I) Enhances GLP-1 Stimulated cAMP Production**

[00149] In this example, the respective effects of a series of compounds of formula (I), including compounds 1 (or N55), 12, 14, 18, and a racemic mixture of compounds 16 and 17, on GLP-1 induced cAMP production in RINm5F cells were investigated, and results are provided in FIG 1A to 1E. The data indicated that each of the test compounds may enhance the GLP-1R signaling (i.e., GLP-1 induced cAMP production) in a dose dependent manner (FIG 1A to 1E).

[00150] **Example 3 Characterization of Compound 1 (N55)**

[00151] **3.1 Compound 1 enhances GLP-1R signaling**

[00152] Among the compounds of formula (I) tested in example 2, compound 1 (or N55) seemed to possess the most potency and was chosen for further study in this example, results are illustrated in FIGs 2 and 3.

[00153] GLP-1 induced cAMP production in a dose dependent and saturable manner, with an EC₅₀ of 2.4 nM (FIG 2, panel A). Compound 1 enhanced cAMP production by shifting the dose-response curve to the left > 10-fold, and

reduced the EC₅₀ of GLP-1 by a factor of 40, as the concentration of compound 1 increased from 0.8 μ M to 26 μ M (FIG 2, panel A). Compound 1 increased the potency of GLP-1 in a dose dependent and saturable manner, with an EC₅₀ of 3.7 μ M (FIG 2, panel B).

5 [00154] To further elucidate the action of compound 1, GLP-1 receptor endocytosis was performed, and results are provided in FIG 3.

[00155] It was found that compound 1 at a concentration of 7.7 μ M significantly shifted the dose-response curve of GLP-1 titration to the left and reduced EC₅₀ to 0.27 nM (FIG 3, panel A). The effects of titration of compound 1 (N55) on
10 GLP-1R endocytosis elicited by 1 nM GLP-1 indicated that compound 1 (N55) facilitated GLP-1 stimulation of receptor endocytosis in a dose-dependent and saturable manner (FIG 3, panel B). EC₅₀ required to enhance receptor endocytosis by 1 nM GLP-1 was 0.87 μ M.

[00156] **3.2 Compound 1 Facilitates GLP-1-elicited insulin release from**
15 **RINm5F cells**

[00157] As compound 1 enhanced the potency of GLP-1 through cAMP production, its effect on subsequent insulin release from pancreatic β -cell line RINm5F cells was investigated.

[00158] It was found that 2 nM GLP-1 consistently stimulated a low level of
20 insulin release from RINm5F cells, and the response was significantly enhanced by the addition of 7.7 μ M of compound 1, although compound 1 alone did not trigger any insulin release (FIG 4). Forskolin was included in this example as a positive control, as it also resulted in the production of cAMP, which led to subsequent insulin release from RINm5F cells.

25 [00159] **3.3 Comparison of Compound 1 with other fatty acids on the potentiation of GLP-1 induced cAMP production**

[00160] It is known that the GLP-1 induced cAMP production may be potentiated by various types of fatty acids, accordingly, their effects were respectively compared with that of compound 1, and results are summarized in
30 Table 1.

[00161] Among 30 fatty acids that were tested in Table 1, only 3 of them (i.e., eicosanpentaenoyl ethanolamide, linoleoyl ethanolamide, and α -linolenoyl ethanolamide) had activities comparable to that of compound 1 (i.e., about 90% of the activity of compound 1); whereas the efficacies of most fatty acids were in
 5 the lower range of that of compound 1 (i.e., 10 to 35% of the activity of compound 1).

[00162] Table 1

Name of Compound	Activity% of compound 1
Compound 1 (N55)	100
9(E), 11(E)-conjugated linoleic acid	30
10(E), 12(Z)-conjugated linoleic acid	30
Linoelaidic acid	30
Eicosapentaenoic acid	60
Docosahexaenoic acid	60
α -linolenic acid	15
9(Z), 11(E)-conjugated linoleic acid	25
Methyl linolelaidate	30
γ -linoleic acid methyl ester	25
linolenic acid methyl ester	15
linoleic acid methyl ester	30
11-trans-octadecenoic acid	10
Cis- octadecenoic acid	25
Oleic acid	35
Methyl cis,cis-9,12-octadecadienoate	15
Methyl γ -linolenate	20
Docosahexaenoyl ethanolamide	20
Docosahexaenoyl serotonin	15
Docosahexaenoyl glycine	15
1-monolinolein	80
Ethyl linoleate	60
Eicosapentaenoyl ethanolamide	90
Eicosapentaenoyl serotonin	20
Linoleoyl glycine	80
N-(α -linolenoyl) tyrosine	70
Linoleoyl ethanolamide	90
α -linolenoyl ethanolamide	90
4-hydroxyisoleucine	<10

[00163] 3.4 Compound 1 Does Not Affect Cell Viability

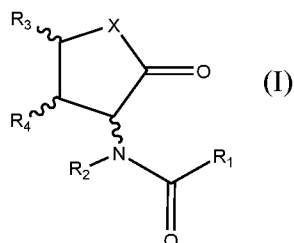
10 [00164] The effect of compound 1 on cell viability was investigated in this example by comparing with that of other agents (e.g., endocannabinoid-like lipids, and anticancer agent), and results are depicted in FIG 5.

[00165] It was found that within the test concentration from 0.78 to 100 μM , compound 1, 2-oleoylglycerol and oleoylethanolamide did not exhibit detectable cytotoxicity, however, cisplatin results in cell death at a concentration of 50 μM , and exhibit an IC_{50} of 6.7 μM (FIG 5).

- 5 [00166] It will be understood that the above description of embodiments is given by way of example only and that various modifications may be made by those with ordinary skill in the art. The above specification, examples and data provide a complete description of the structure and use of exemplary embodiments of the invention. Although various embodiments of the invention
- 10 have been described above with a certain degree of particularity, or with reference to one or more individual embodiments, those with ordinary skill in the art could make numerous alterations to the disclosed embodiments without departing from the spirit or scope of the present disclosure.

WHAT IS CLAIMED IS:

1. A compound of formula (I),



5

wherein,

X is O or S;

R₁ is H or ;

R₂ is H or a nitrogen protecting group;

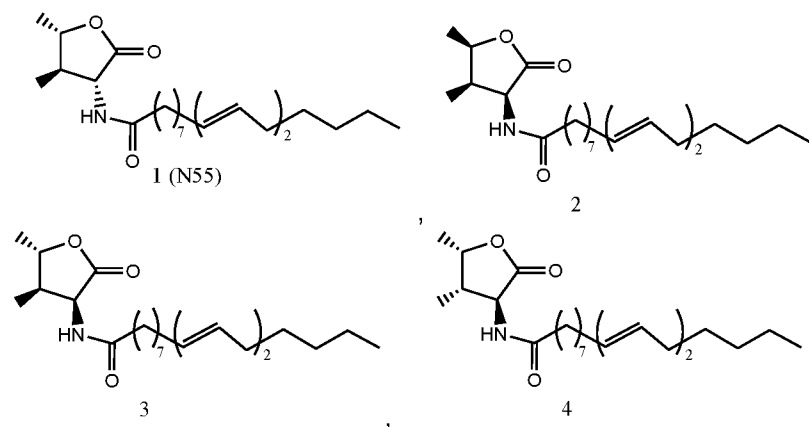
- 10 R₃ and R₄ are independently H, halogen, optionally substituted alkyl, or alkenyl; or R₃ and R₄ are taken together to form an optionally substituted 6-membered carbocycle or heterocycle;

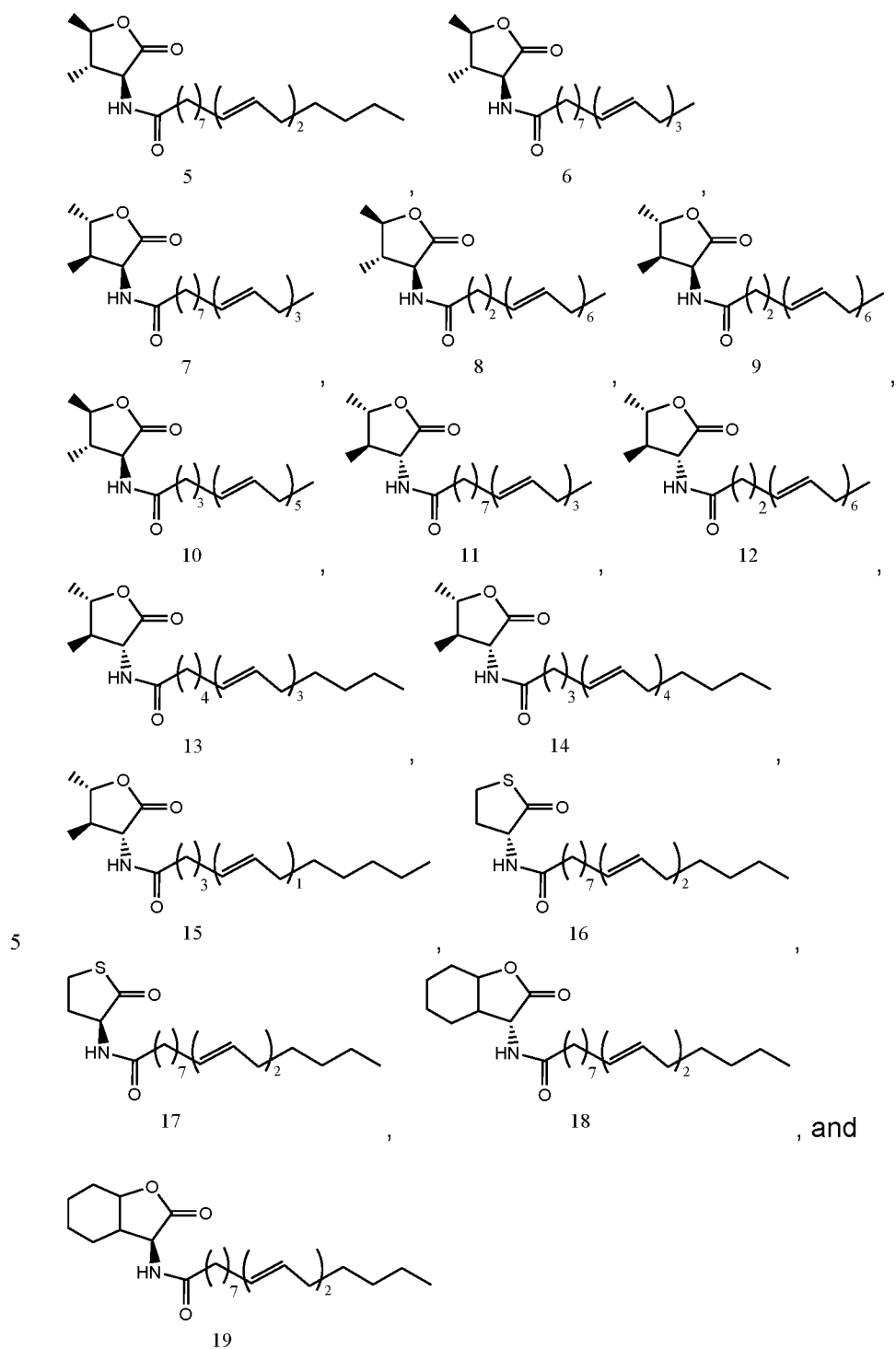
R' is H or optionally substituted alkyl; and

n and m are independently an integral between 1 to 10.

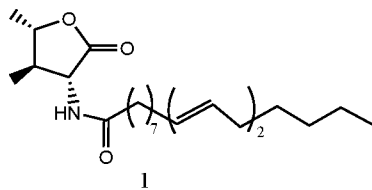
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2. The compound of claim 1, wherein the compound is selected from the group consisting of:





10 3. The compound of claim 1, wherein the compound is

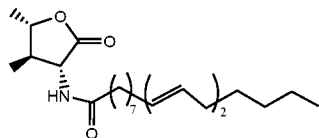


4. A kit, comprising:

a first container containing a blood sugar reducing agent; and

5 a second container containing the compound of claim 1.

5. The kit of claim 4, wherein the compound of formula (I) is



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6. The kit of claim 4, wherein the blood sugar reducing agent is selected from the group consisting of, alpha-glucosidase inhibitor, biguanide, dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor, 15 sulfonyleurea, and thiazolidinedione.

7. The kit of claim 6, wherein the alpha-glucosidase inhibitor is acarbose or miglitol.

20 8. The kit of claim 6, wherein the biguanide is metformin.

9. The kit of claim 6, wherein the dopamine agonist is bromocriptine.

10. The kit of claim 6, wherein the DPP-4 inhibitor is alogliptin, linagliptin, 25 saxagliptin, sitagliptin, or simvastatin.

11. The kit of claim 6, wherein the GLP-1 is lixisenatide, albiglutide, dulaglutide, exenatide, or liraglutide.

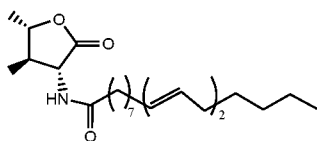
12. The kit of claim 6, wherein the SGLT 2 inhibitor is dapagliflozin, canagliflozin,
5 or empagliflozin.

13. The kit of claim 6, wherein the sulfonylurea is glimepiride, gliclazide, glipizide, glyburide, chlorpropamide, tolazamide, or tolbutamide.

10 14. The kit of claim 6, wherein the thiazolidinedione is pioglitazone or rosiglitazone.

15. A method for treating diseases and/or disorders associated with hyperglycemia in a subject comprising administering to the subject a
15 therapeutically effective amount of the compound of claim 1, so as to reduce the blood sugar level of the subject.

16. The method of claim 15, wherein the compound is



20

17. The method of claim 15, further comprising administering to the subject a blood sugar reducing agent before, together with, or after the administration of the compound of claim 1.

25

18. The method of claim 17, wherein the blood sugar reducing agent is selected from the group consisting of, alpha-glucosidase inhibitor, biguanide, dopamine agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1), meglitinide, sodium glucose transporter (SGLT) 2 inhibitor,

sulfonylurea, and thiazolidinedione.

19. The method of claim 18, wherein the alpha-glucosidase inhibitor is acarbose or miglitol.

5

20. The method of claim 18, wherein the biguanide is metformin.

21. The method of claim 18, wherein the dopamine agonist is bromocriptine.

10 22. The method of claim 18, wherein the DPP-4 inhibitor is alogliptin, linagliptin, saxagliptin, sitagliptin, or simvastatin.

23. The method of claim 18, wherein the GLP-1 is lixisenatide, albiglutide, dulaglutide, exenatide, or liraglutide.

15

24. The method of claim 18, wherein the SGLT 2 inhibitor is dapagliflozin, canagliflozin, or empagliflozin.

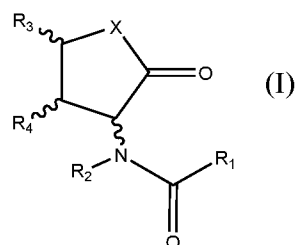
20 25. The method of claim 18, wherein the sulfonylurea is glimepiride, gliclazide, glipizide, glyburide, chlorpropamide, tolazamide, or tolbutamide.

26. The method of claim 18, wherein the thiazolidinedione is pioglitazone or rosiglitazone.

25 27. The method of claim 15, wherein the diseases and/or disorders associated with hyperglycemia is diabetes, obesity, impaired glucose tolerance, impaired fasting glycemia (IFG), hyperinsulinemia, hyperlipidemia, hyper-cholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema,
30 hyperuricemia, gout or diabetic complication.

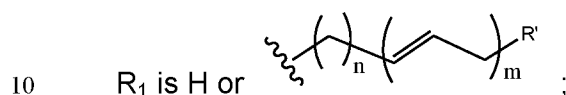
28. The method of claim 27, wherein the diabetic complication is retinopathy, neuropathy, nephropathy, ulcer, or macroangiopathy.

29. Compound of formula (I) and blood sugar reducing agent for use in the
5 treatment of diseases and/or disorders associated with hyperglycemia,



wherein,

X is O or S;



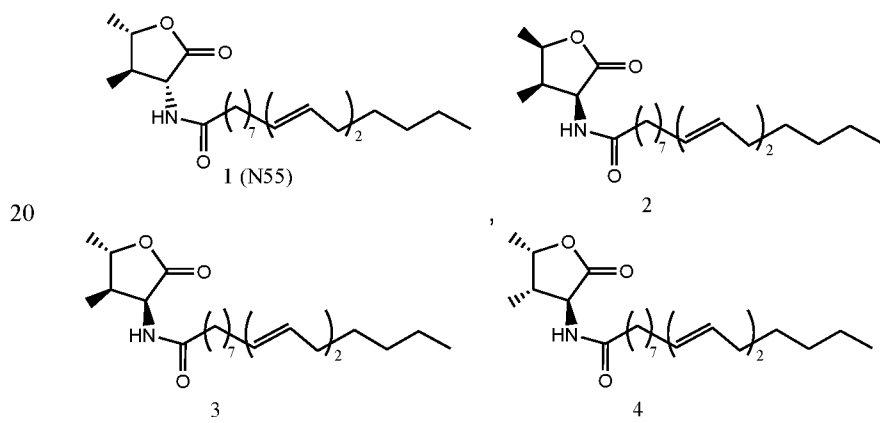
R₂ is H or a nitrogen protecting group;

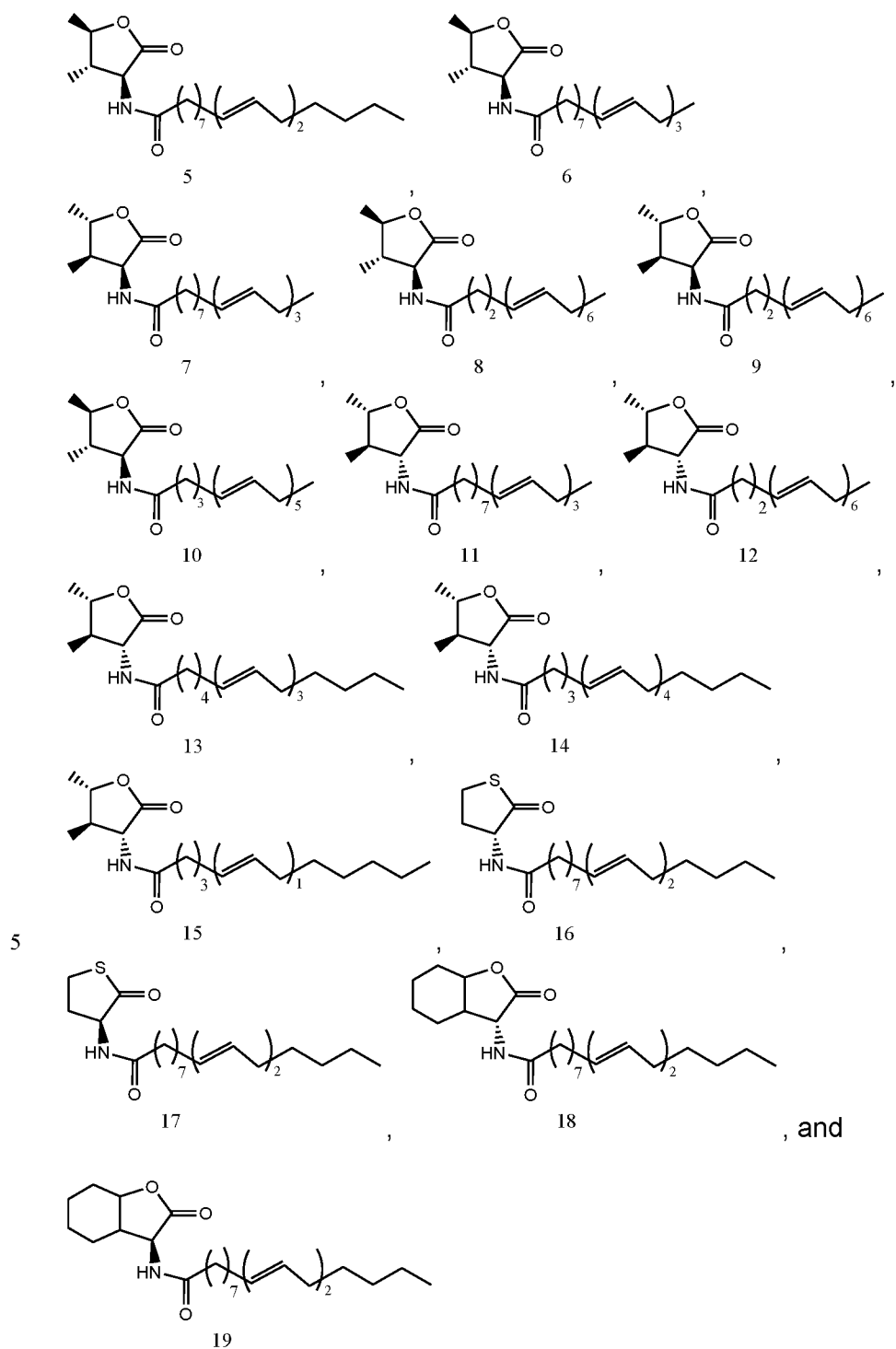
R₃ and R₄ are independently H, halogen, optionally substituted alkyl, or alkenyl; or R₃ and R₄ are taken together to form an optionally substituted 6-membered carbocycle or heterocycle;

15 R' is H or optionally substituted alkyl; and

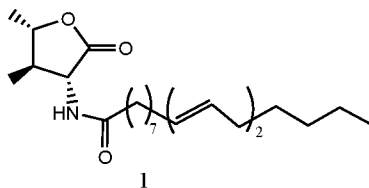
n and m are independently an integral between 1 to 10.

30. Compound of formula (I) and blood sugar reducing agent for use of claim 29, wherein the compound is selected from the group consisting of:





31. Compound of formula (I) and blood sugar reducing agent for use of claim 30,



wherein the compound is

32. Compound of formula (I) and blood sugar reducing agent for use of claim 29,
 wherein the diseases and/or disorders associated with hyperglycemia is
 5 diabetes, obesity, impaired glucose tolerance, impaired fasting glycemia
 (IFG), hyperinsulinemia, hyperlipidemia, hyper-cholesterolemia,
 hypertriglyceridemia, lipid metabolism disorder, atherosclerosis,
 hypertension, congestive heart failure, edema, hyperuricemia, gout or
 diabetic complication.

10

33. Compound of formula (I) and blood sugar reducing agent for use of claim 32,
 wherein the diabetic complication is retinopathy, neuropathy, nephropathy,
 ulcer, or macroangiopathy.

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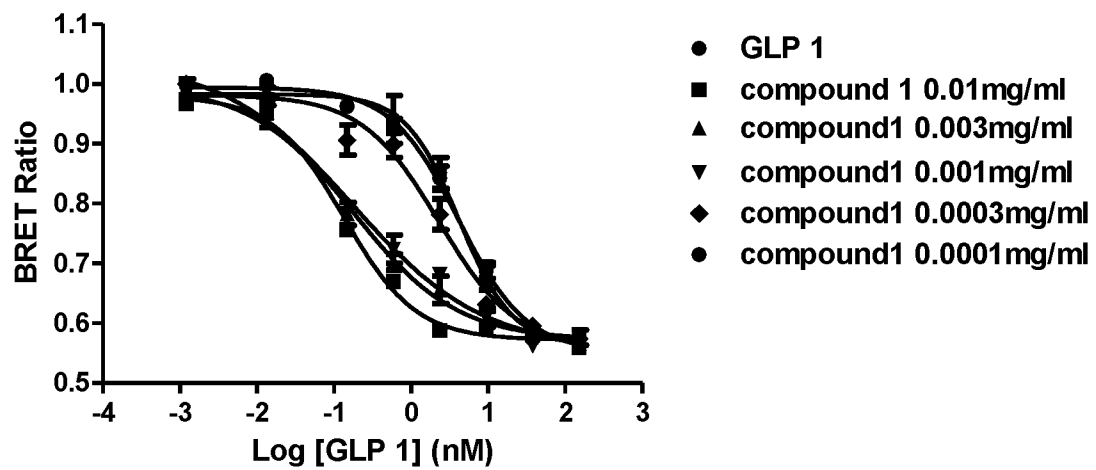


FIG 1A

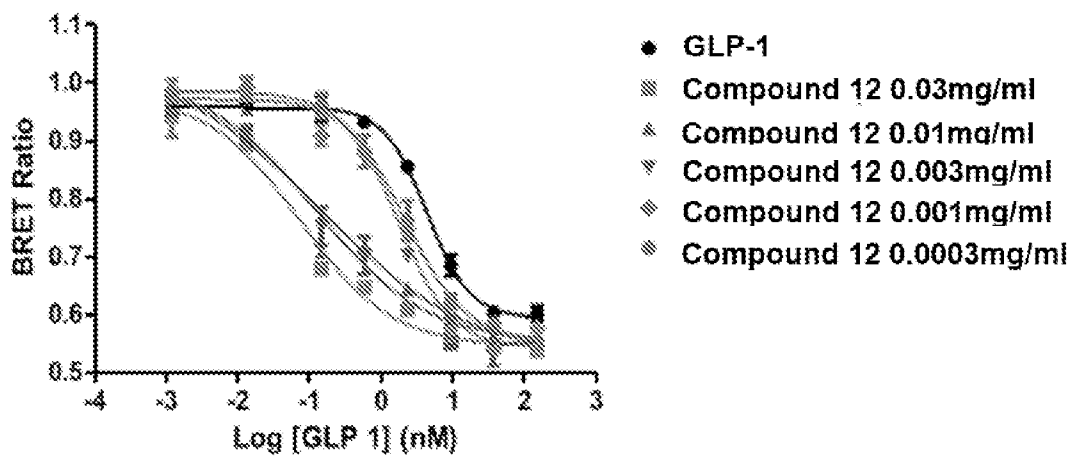


FIG 1B

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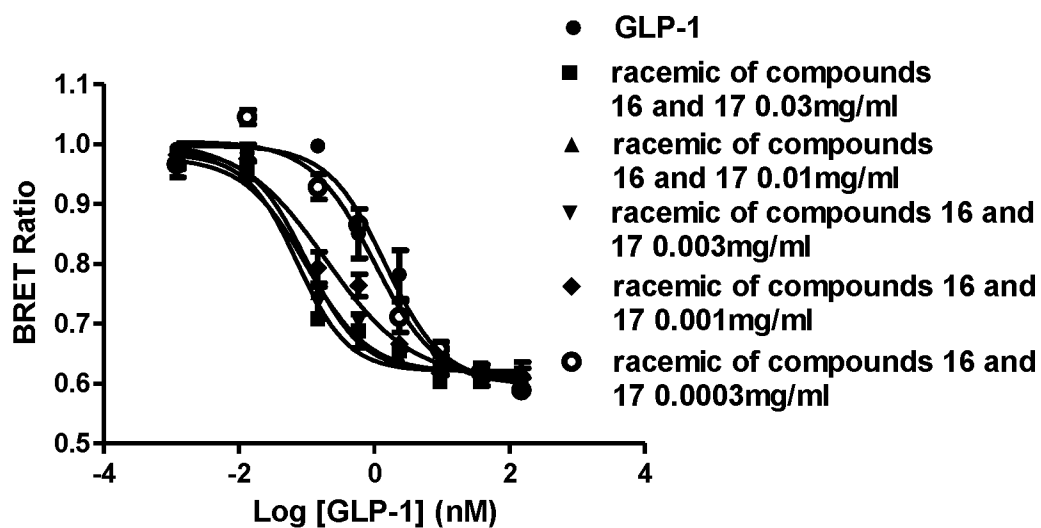


FIG 1C

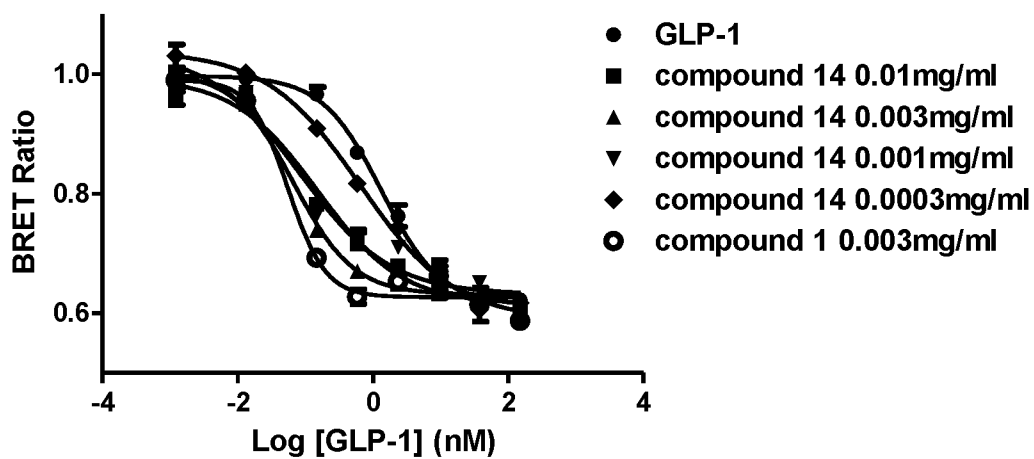


FIG 1D

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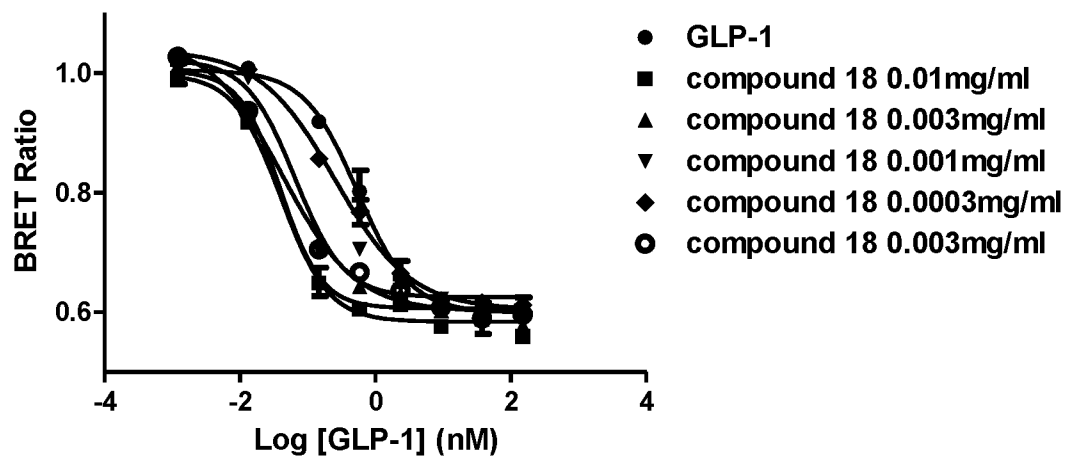
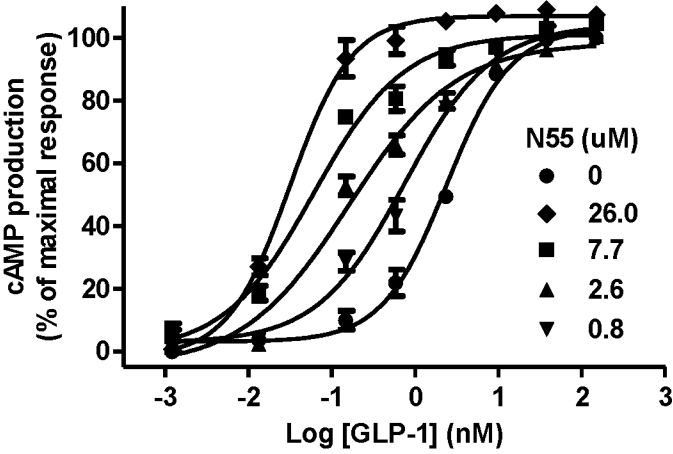


FIG 1E

(A)



(B)

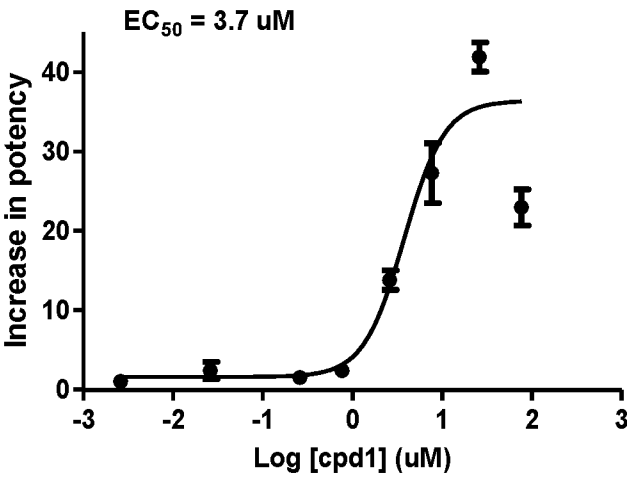
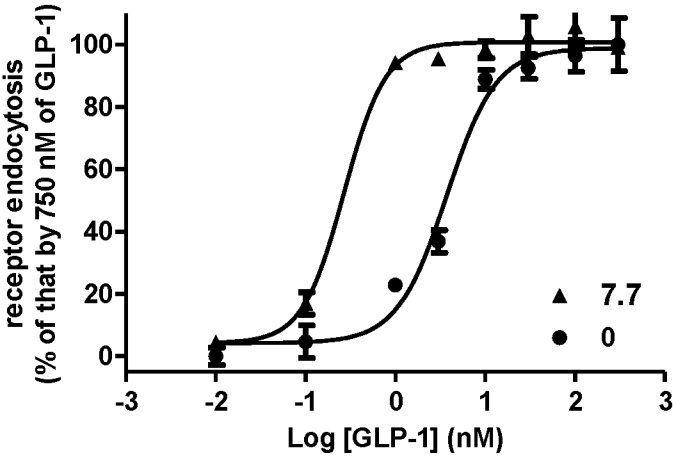


FIG 2

(A)



(B)

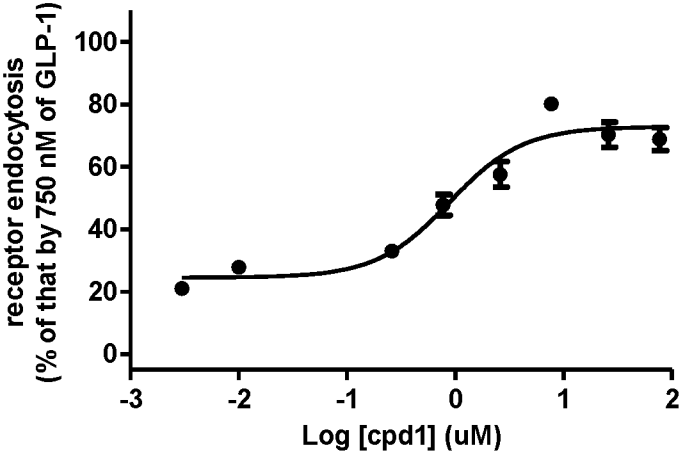


FIG 3

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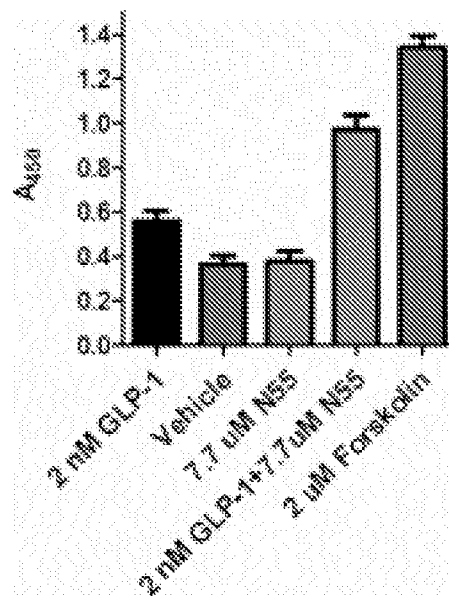


FIG 4

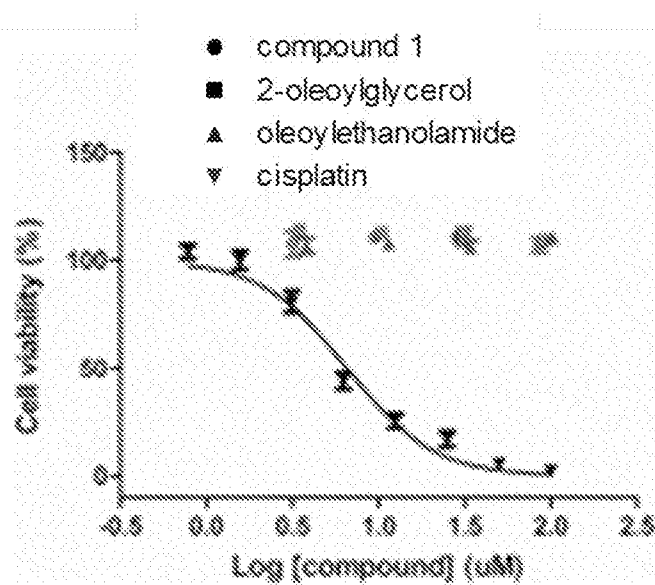


FIG 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/40225

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/365, 31/341; A61P 3/08 (2016.01)

CPC - A61K 31/365, 31/341

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): A61K 8/42, 31/365, 31/34, 31/341, 31/381, 31/40; A61P 3/04, 3/08 (2016.01)

CPC: A61K 8/42, 31/365, 31/34, 31/341, 31/381, 31/40 (2016.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer; Google Scholar; Pubmed; EBSCO; SureChEMBL; Liang, Academia Sinica, Chien, King, Lin, Cheng, diabetes, simvastatin, N-[(3R,4S,5S)-4,5-dimethyl-2-oxoxolan-3-yl]formamide, N-[(3S,4R,5S)-4,5-dimethyl-2-oxoxolan-3-yl]acetamide, dopamine agonist, (9Z)-N-(2-oxoxolan-3-yl)hexadec-9-enamide, Lactone, Linoleic acid, blood sugar, reducing, elevation, kit, vessel, package, amide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0221210 A1 (DAHMEN, P et al) 7 August 2014; claim 3	1
Y	US 2010/0048545 A1 (JETTE, L et al) 25 February 2010; abstract; paragraphs [0040], [0104], [0107], [0251]-[0252], [0256], [0320], [0329]-[0330], [0334], [0644]	1-33
Y	WO 2009/109973 A2 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM LTD) 11 September 2009; page 38, lines 5-20; page 42, lines 20-25	1-5, 15-16, 29-31
Y	WO 2008/154743 A1 (INNODIA INC) 24 December 2008; paragraphs [0035], [0077]	1, 4, 6-15, 17-29, 32-33
Y	KIM, JS et al. Inhibition of Alpha-glucosidase and Amylase by Luteolin, a Flavonoid. Bioscience, Biotechnology and Biochemistry, Vol. 64, No. 11, 2000, pp. 2458-2461; page 2458, column 1, paragraph 1; page 2460, column 1, paragraph 2	7, 19
Y	GAZIANO, JM et al. Randomized Clinical Trial of Quick-Release Bromocriptine Among Patients With Type 2 Diabetes on Overall Safety and Cardiovascular Outcomes. Diabetes Care, Vol. 33, 2010, pp. 1503-1508; abstract	9, 21
Y	KOH, KK et al. Vascular and Metabolic Effects of Combined Therapy with Ramipril and Simvastatin in Patients with Type 2 Diabetes. Hypertension, Vol. 45, 2005, pp. 1088-1093; abstract	10, 22

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* 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

19 August 2016 (19.08.2016)

Date of mailing of the international search report

07 SEP 2016

Name and mailing address of the ISA/

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Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/40225

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SEINO, Y et al. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes, Obesity and Metabolism, Vol. 14, 2012, pp. 910–917; abstract	11, 23
Y	LIST, JF et al. Sodium-Glucose Cotransport Inhibition with Dapagliflozin in Type 2 Diabetes. Diabetes Care, Vol. 32, 2009, pp. 650–657; abstract	12, 24
Y	ANTONETTI, et al. Perspectives in Diabetes Diabetic Retinopathy Seeing Beyond Glucose-Induced Microvascular Disease. Diabetes, Vol. 55, September 2006, pp. 2401–2411; abstract; page 2403; column 2, paragraph 3; paragraph 2406, column 1, paragraph 2	28, 33