COMPOSITIONS AND METHODS FOR TREATMENT OF INSULIN RESISTANCE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional application No. 62/639,880, filed March 7, 2018, the entire disclosure of which is incorporated herein by reference.

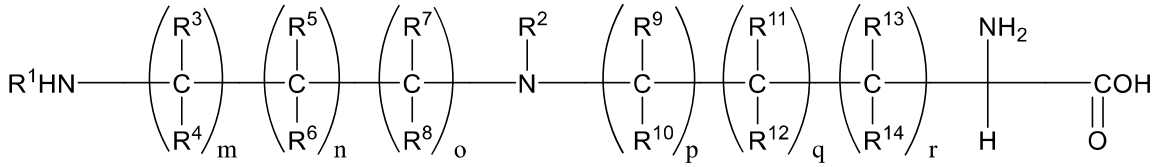
SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 1, 2019 is named 035926_0501_00_WO_587256_ST25.txt and is 875 bytes in size.

SUMMARY

[0003] In examples, this disclosure relates to methods of treating or preventing type 2 diabetes, pre-diabetes and conditions characterized by an increase in the levels of A1C, glucose, insulin, homeostasis model of assessment of insulin resistance (HOMA-IR), oxidative stress in adipose tissue, and carbonylation of GLUT4 comprising administering an effective amount of a compound of Formula I-III as described herein, to a subject in need thereof.

[0003a] In one aspect, the present disclosure refers to the use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating type 2 diabetes in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

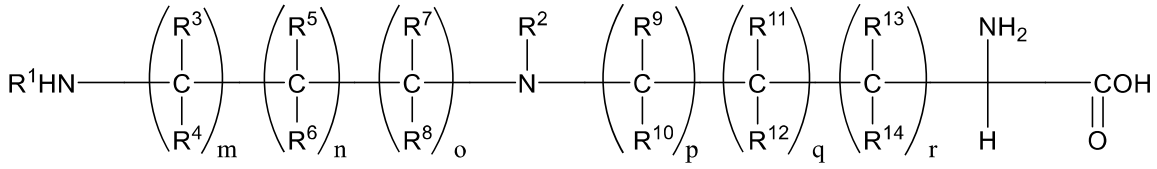
R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
o is 0, 1, 2, 3 or 4;
p is 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4; and
r is 0, 1, 2, 3 or 4.

[0003b] In another aspect, the present disclosure refers to the use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating pre-diabetes in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

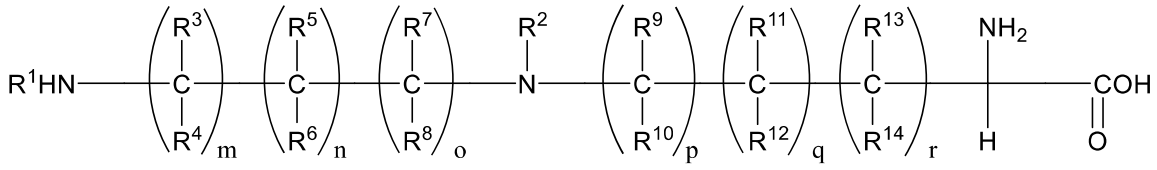
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0003c] In yet another aspect, the present disclosure refers to the use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating a condition in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
o is 0, 1, 2, 3 or 4;
p is 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4; and
r is 0, 1, 2, 3 or 4, and

wherein the condition is characterized by an increase in a measurement selected from the group consisting of A1C, glucose, insulin, homeostasis model of assessment of insulin resistance (HOMA-IR), oxidative stress in adipose tissue, and carbonylation of GLUT4.

DESCRIPTION OF THE DRAWINGS

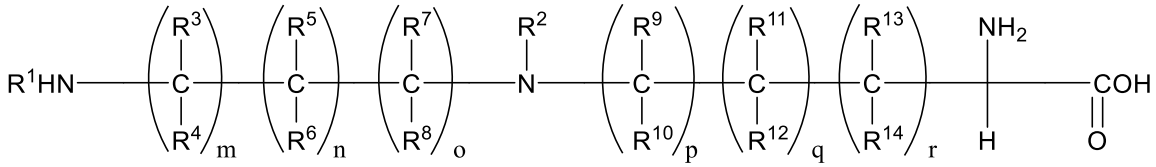
[0001] FIG. 1 demonstrated the stoichiometry of GLUT4 carbonylation in adipose tissue from obese non-diabetic (n=4), obese pre-diabetic (n=4), and obese diabetic (n=12) subjects (* $p < 0.005$).

[0002] FIG. 2 provides a graphical depiction of the correlation between adipose tissue GLUT4 carbonylation and HbA1C.

[0003] FIG. 3 provides typical MRM data showing an increase in the transitions of HNE-induced K264-HNE adduct (left panel) which were used to calculate the amounts of carbonylated GLUT4 (right panel). Four transitions of the GLUT4 peptide found in humans are shown. The sequence of the carbonylated GLUT4 peptide LTGWADVSGVLAELKDEK-4HNE (SEQ ID NO:1) is depicted.

Claims

1. Use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating type 2 diabetes in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
o is 0, 1, 2, 3 or 4;
p is 1, 2, 3 or 4;
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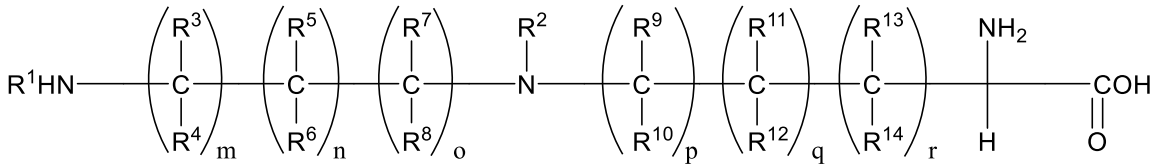
2. The use of claim 1, wherein a symptom of type 2 diabetes is treated.

3. The use of claim 2, wherein the symptom is selected from the group consisting of increased A1C level, increased fasting blood glucose, impaired glucose tolerance increased blood pressure, and increased blood glucose level.

4. The use of claim 1, wherein the therapeutically effective amount of a compound of Formula I is about 1 mg/day to about 1,000 mg/day.

5. The use of claim 1, wherein the compound of Formula I is to be administered with one or more additional therapeutic agent.

6. Use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating pre-diabetes in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
o is 0, 1, 2, 3 or 4;
p is 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4; and
r is 0, 1, 2, 3 or 4.

7. The use of claim 6, wherein the subject has been diagnosed with impaired glucose tolerance, impaired fasting glucose, or insulin resistance.

8. The use of claim 6, wherein a risk of developing diabetes is reduced.

9. The use of claim 6, wherein a risk of developing a disease selected from the group consisting of kidney disease, diabetic retinopathy, heart attack and stroke, is reduced.

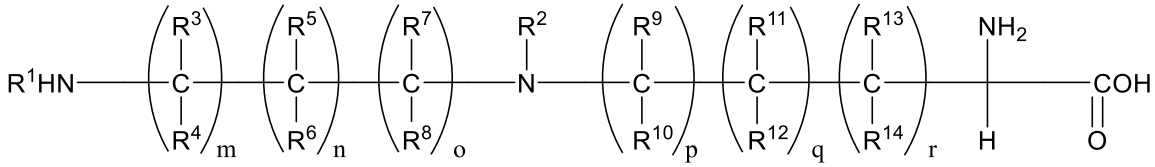
10. The use of claim 6, wherein a symptom of pre-diabetes is treated.

11. The use of claim 10, wherein the symptom is selected from the group consisting of increased A1C level, increased fasting blood glucose, impaired glucose tolerance, increased blood pressure, and increased blood glucose level.

12. The use of claim 6, wherein the therapeutically effective amount of a compound of Formula I is about 1 mg/day to about 1,000 mg/day

13. The use of claim 6, wherein the compound of Formula I is to be administered with one or more additional therapeutic agent.

14. Use of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

in the manufacture of a medicament for preventing or treating a condition in a subject in need thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and

substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
o is 0, 1, 2, 3 or 4;
p is 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4; and
r is 0, 1, 2, 3 or 4, and

wherein the condition is characterized by an increase in a measurement selected from the group consisting of A1C, glucose, insulin, homeostasis model of assessment of insulin resistance (HOMA-IR), , oxidative stress in adipose tissue, and carbonylation of GLUT4.

15. The use of claim 14, wherein the subject has been diagnosed with impaired glucose tolerance, impaired fasting glucose, insulin resistance, pre-diabetes, or type 2 diabetes.

16. The use of claim 14, wherein a risk of developing pre-diabetes or type 2 diabetes is reduced.

17. The use of claim 13, wherein a risk of developing a disease selected from the group consisting of kidney disease, diabetic retinopathy, heart attack and stroke, is reduced.

18. The use of claim 14, wherein a symptom of the condition is treated.

19. The use of claim 18, wherein the symptom is selected from the group consisting of increased A1C level, increased fasting blood glucose, impaired glucose tolerance, increased blood pressure, and increased blood glucose level.

20. The use of claim 14, wherein the therapeutically effective amount of a compound of Formula I is about 1 mg/day to about 1,000 mg/day.

21. The use of claim 14, wherein the compound of Formula I is to be administered with one or more additional therapeutic agent.