[004] Current treatments for diabetes include: insulin, insulin secretagogues, such as sulphonylureas, which increase insulin production from pancreatic β-cells; glucose-lowering effectors, such as metformin which reduce glucose production from the liver; activators of the peroxisome proliferator-activated receptor-γ (PPAR-γ), such as the thiazolidinediones, which enhance insulin action; dipeptidyl peptidase-4 (DPP-4) inhibitors which inhibit the degradation of GLP-1 and α-glucuronidase inhibitors which interfere with gut glucose production. However, there are some deficiencies associated with these treatments. For example, sulphonylureas and insulin injections can be associated with hypoglycemia and weight gain. Responsiveness to sulphonylureas is often lost over time. An increased relative risk of pancreatic cancer and to a lesser extent other neoplasms has been linked to the use of DPP-4 inhibitors. Gastrointestinal problems are observed with metformin and α-glucosidase inhibitors. Finally, PPAR-γ agonists may cause increase weight and edema.

[005] The present invention aims to address the needs for new treatment methods, compounds and pharmaceutical compositions for treating patients with diabetes and for treating patients with one or more disorders and conditions associated with abnormal levels of glucose, insulin, ketone bodies, plasma lipoprotein, triglycerides and the like.

[006] International PCT publication WO 2014/138906 is a patent application filed previously by the present Applicant. That patent document describes compounds whose structure is related to the structure of the compounds of the present invention. However, that prior patent application is concerned with the treatment of fibrosis, not diabetes.

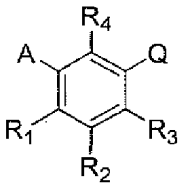
[007] Additional features of the invention will be apparent from a review of the disclosure, figures and description of the invention herein.

BRIEF SUMMARY OF THE INVENTION

[008] The present disclosure relates to the pharmaceutical use of compounds according to Formula I as defined herein, and pharmaceutically acceptable salts thereof.

[009] The present disclosure relates to the use of compounds and compositions for the prevention and/or treatment of diabetes. The present disclosure also concerns compounds according to Formula I as defined herein, and pharmaceutically acceptable salts thereof.

[0010] An embodiment relates to a method for preventing and/or treating diabetes, said method comprising the step of administering to a subject in need thereof a compound represented by Formula I as defined herein, or a pharmaceutically acceptable salt thereof. In one aspect, there is provided a compound represented by Formula I or a pharmaceutical acceptable salt thereof for the preparation of a medicament for preventing and/or treating diabetes, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day, wherein the Formula I is :



Formula I

wherein

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_1 is H, F or OH;

R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_3 is H, F, OH or CH_2Ph;

R_4 is H, F or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,
2) $CH(CH_3)C(O)OH$,
3) $C(CH_3)_2C(O)OH$,
4) $CH(F)-C(O)OH$,
5) $CF_2-C(O)OH$, or
6) $C(O)-C(O)OH$.

[0011] According to particular embodiments, the compounds and compositions of the invention relates to the prevention and/or treatment of Type I diabetes, Type II diabetes, Type III diabetes (Alzheimer), maturity-onset diabetes of the young, latent autoimmune diabetes of adults (LADA), gestational diabetes, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, diabetic neuropathy, diabetic retinopathy, atherosclerosis, sexual dysfunction, and metabolic syndrome. In one particular embodiment, the diabetes is Type II diabetes. In another particular embodiment, the diabetes is Type I diabetes.

[0012] In an embodiment, the present disclosure relates to methods wherein administration of Formula I as defined herein, and/or pharmaceutically acceptable salts thereof, results in one or more of the following biological activities the subject: an increase in insulin secretion; an increase in insulin sensitivity; a decrease in insulin resistance; a decrease in blood glucose level; and a decrease of blood triglyceride level.

[0013] In another aspect, there is provided a use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, for the preparation of a medicament for modulating glucose, insulin and/or triglyceride levels in a subject in need thereof, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day. In an embodiment, the present disclosure relates to a method for modulating glucose, insulin and/or triglyceride levels in a subject in need thereof, comprising the step of administering to the subject a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein. In some embodiments, administration of the compound reduces blood glucose level. In some embodiments, the purpose of the method is for maintaining or increasing insulin level, and administration of the compound maintains or increases insulin level in a subject requiring protection and/or regeneration of pancreatic islets.

[0014] In another aspect, there is provided a use of a compound represented by Formula I or a pharmaceutical acceptable salts thereof as defined herein, for the preparation of a medicament for increasing insulin secretion and/or increasing insulin sensitivity and/or decreasing insulin resistance in a subject in need thereof, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day. In an embodiment, the present disclosure relates to a method for increasing insulin secretion and/or increasing insulin sensitivity and/or decreasing insulin resistance in a subject in need thereof,

comprising the step of administering to the subject a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein. In one embodiment the subject is afflicted by hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, dyslipidemia and/or loss of pancreatic function. In another embodiment, the compound is administered concomitantly with a second therapeutic agent (e.g. a compound for lowering or modulating blood glucose level such as metformin or is a thiazolidinedione).

[0015] In another aspect, there is provided a use of a compound represented by Formula I or a pharmaceutical acceptable salts thereof as defined herein, for reducing blood triglyceride in a subject in need thereof, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day.In an embodiment, the present disclosure relates to a method for reducing blood triglyceride in a subject in need thereof, comprising the step of administering to the subject a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein, wherein the compound reduces blood triglyceride level. In one embodiment the subject is afflicted by diabetic dyslipidemia and/or metabolic syndrome.

[0016] The present disclosure relates to the use of a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein, for the manufacture of a medicament for preventing and/or treating diabetes.

[0017] The present disclosure also relates to a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein, for use in the prevention or treatment of diabetes in a subject in need thereof.

[0018] The present disclosure also relates to a pharmaceutical composition comprising: (i) a compound of Formula I, or a pharmaceutical acceptable salt thereof, as defined herein; and (ii) a second therapeutic agent for lowering or modulating blood glucose level. In one embodiment the second therapeutic agent is metformin or thiazolidinedione. Preferably, the composition is adapted for an oral administration.

[0019] Further aspects of the invention will be apparent to a person skilled in the art from the following description, claims, and generalizations herein.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **Figure 1** is a bar graph showing that Compound I reduces blood glucose level down to normal level in uninephrectomized db/db mice, according to Example 3.

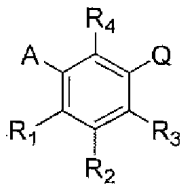
[0021] **Figure 2** is a bar graph showing that Compound I reverses the fall of insulin secretion in uninephrectomized db/db mice, according to Example 3.

[0022] **Figure 3** is a bar graph showing effect of Compound I on the Glucose/Insulin Ratio at Day 33 in uninephrectomized db/db mice, according to Example 3.

[0023] **Figure 4** is a bar graph showing effect of Compound I on the Glucose/Insulin Ratio at Day 105 in uninephrectomized db/db mice, according to Example 3.

CLAIMS:

1. A use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof for the preparation of a medicament for preventing and/or treating diabetes, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day, wherein the Formula I is :



Formula I

wherein

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_1 is H, F or OH;

R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_3 is H, F, OH or CH_2Ph;

R_4 is H, F or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,
2) $CH(CH_3)C(O)OH$,
3) $C(CH_3)_2C(O)OH$,
4) CH(F)-C(O)OH,
5) CF_2-C(O)OH, or
6) C(O)-C(O)OH.

2. The use of claim 1, wherein the dose is between 0.1 to 1.0 mg/kg per day.

3. The use of claim 1 or 2, wherein A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, or C_6 alkenyl.

4. The use of any one of claims 1-3, wherein R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, or C_6 alkenyl.

5. The use of any one of claims 1-4, wherein R_3 is H, OH or CH_2Ph.

6. The use of any one of claims 1-5, wherein R_4 is H.

7. The use of any one of claims 1-6, wherein Q is $(CH_2)_mC(O)OH$, and wherein m is 1 or 2.

8. The use of any one of claims 1-6, wherein Q is $(CH_2)_mC(O)OH$, and wherein m is 1.

9. The use of claim 1, wherein:

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, or C_6 alkenyl;

R_1 is H or OH;

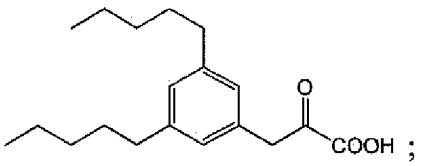
R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, or C_6 alkenyl;

R_3 is H, OH or CH_2Ph;

R_4 is H; and

Q is $(CH_2)_mC(O)OH$ wherein m is 1 or 2.

10. The use of claim 1 or 2, wherein said compound is represented by one of the following structures:



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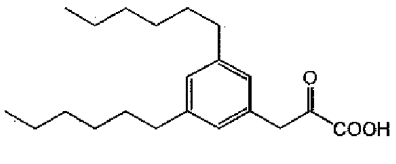

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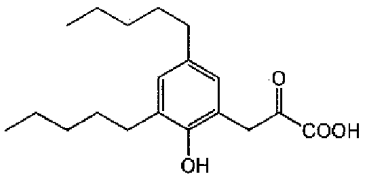

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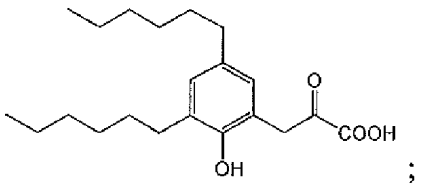
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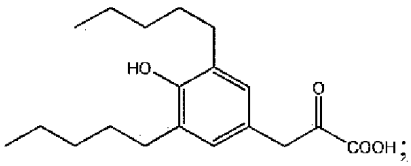
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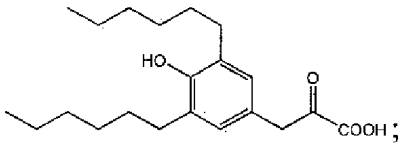
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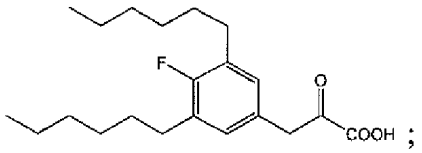
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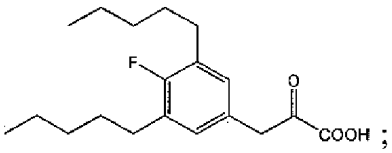
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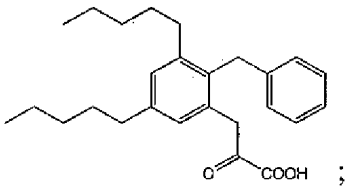
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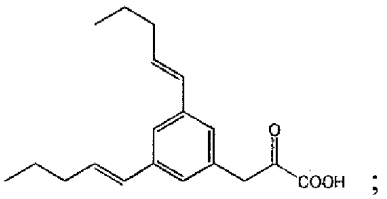
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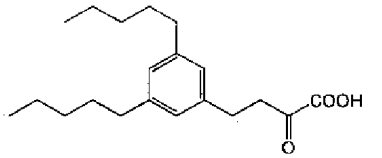
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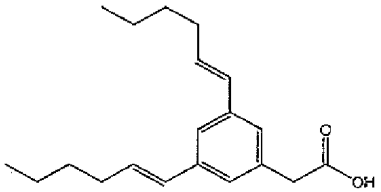
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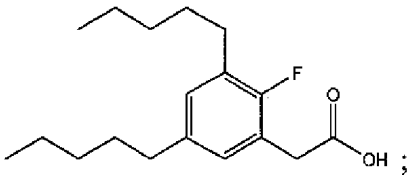
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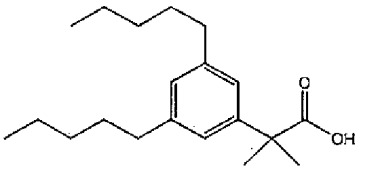
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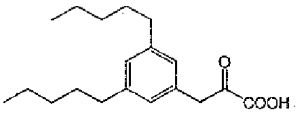
or a pharmaceutical acceptable salt thereof.

11. The use of claim 10, wherein said compound is represented by the following structure:



or pharmaceutical acceptable salt thereof.

12. The use of any one of claims 1 to 11, wherein the pharmaceutically acceptable salt is a base addition salt comprising a metal counterion selected from the group consisting of sodium, potassium, calcium, magnesium, lithium, ammonium, manganese, zinc, iron, or copper.

13. The use of claim 12, wherein the pharmaceutically acceptable salt is sodium.

14. The use of any one of claims 1-13, wherein said diabetes is Type I diabetes, Type II diabetes, Type III diabetes (Alzheimer), maturity-onset diabetes of the young, latent autoimmune diabetes of adults (LADA), gestational diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, syndrome X, diabetic neuropathy, diabetic retinopathy, atherosclerosis, sexual dysfunction, and metabolic syndrome.

15. The use of claim 14, wherein said diabetes is Type II diabetes.

16. The use of claim 14, wherein said diabetes is Type I diabetes.

17. The use of any one of claims 1-16, wherein medicament is also for:

- increasing insulin secretion;
- increasing insulin sensitivity;
- decreasing insulin resistance;
- decreasing blood glucose level; or
- decreasing blood triglyceride level.

18. The use of claim 17, wherein the medicament is also for reducing blood glucose level, wherein administration of said compound reduces blood glucose level.

19. The use of claim 17, wherein the medicament is also for maintaining or increasing insulin level, wherein administration of said compound maintains or increases insulin level in a subject requiring protection and/or regeneration of pancreatic islets.

20. A use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 13, for the preparation of a medicament for modulating glucose, insulin and/or triglyceride levels in a subject in need thereof, wherein said medicament is for administration of

compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day.

21. The use of claim 20, wherein the dose is between 0.1 to 1.0 mg/kg per day.

22. A use of a compound represented by Formula I or a pharmaceutical acceptable salts thereof as defined in any one of claims 1 to 13, for the preparation of a medicament for increasing insulin secretion and/or increasing insulin sensitivity and/or decreasing insulin resistance in a subject in need thereof, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day.

23. The use of claim 22, wherein the dose is between 0.1 to 1.0 mg/kg per day.

24. The use of any one of claims 1-23, wherein the subject is afflicted by hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, dyslipidemia and/or loss of pancreatic function.

25. The use of any one of claims 1-24, further comprising a second therapeutic agent.

26. The use of claim 25, wherein the second therapeutic agent is a compound for lowering or modulating blood glucose level.

27. The use of claim 25, wherein the second therapeutic agent is metformin or is a thiazolidinedione.

28. A use of a compound represented by Formula I or a pharmaceutical acceptable salts thereof as defined in any one of claims 1 to 13, for reducing blood triglyceride in a subject in need thereof, wherein said medicament is for administration of compound represented by Formula I or a pharmaceutical acceptable salt thereof at a dose of 0.1 to 5 mg/kg per day.

29. The use of claim 28, wherein the dose is between 0.1 to 1.0 mg/kg per day.

30. The use of claim 28 or 29, wherein the subject is afflicted by diabetic dyslipidemia and/or metabolic syndrome.

31. The use of any one of claims 1-30, wherein the composition is for oral administration.