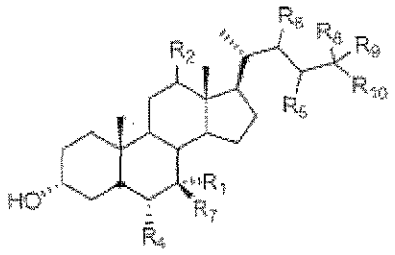
Thus, there is a need for the development of TGR5 modulators for the treatment and/or prevention of various diseases. The present invention has identified compounds that modulate TGR5 as well as methods of using these compounds to treat or prevent disease.

Summary ~~of the Invention~~

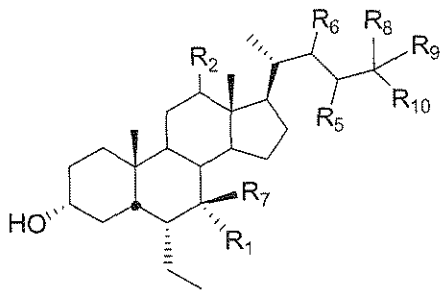
The present ~~invention~~ disclosure relates to TGR5 modulators and their use to treat and/or prevent various diseases. The ~~invention~~ present disclosure relates to compounds according to formula A:



(A),

or a salt, solvate, hydrate, or prodrug thereof. In formula A, variables R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} can be selected from the respective groups of chemical moieties later defined in the detailed description. The present disclosure ~~invention~~ includes a composition comprising a compound of the present disclosure ~~invention~~ or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and at least one pharmaceutically acceptable excipient. The present disclosure ~~invention~~ includes a compound for use in a method of treating or preventing disease in a subject. The present disclosure ~~invention~~ also includes the use of a composition or compound of the present disclosure ~~invention~~ or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a treating or preventing a disease in a subject. In one ~~aspect~~embodiment, the disease is selected from metabolic disease, inflammatory disease, liver disease, autoimmune disease, cardiac disease, kidney disease, cancer, and gastrointestinal disease.

In one aspect of the present disclosure, there is provided a compound of formula III:



(III),

or a salt, hydrate, glycine or taurine amino acid conjugate, or prodrug thereof, wherein:

R_1 is hydrogen, hydroxyl, or halogen;

R_2 is hydrogen or α-hydroxyl;

R_3 is hydroxyl, $NH(CH_2)_mSO_3H$, or $NH(CH_2)_nCO_2H$;

R_5 is unsubstituted C_2-C_6 alkyl, substituted alkyl, or aryl;

R_6 is hydrogen; or

R_5 and R_6 taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms;

R_7 is hydrogen, unsubstituted or substituted alkyl, or hydroxyl;

R_8 is hydrogen, unsubstituted or substituted alkyl;

R_9 is hydrogen, unsubstituted or substituted alkyl; or

R_8 and R_9 taken together with the carbon to which they are attached form a carbonyl;

R_{10} is R_3 or SO_3H;

m is an integer 0, 1, 2, 3, 4, or 5; and

n is an integer 0, 1, 2, 3, 4, or 5.

In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, for use as a medicament.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disease selected from the group consisting of metabolic disease, inflammatory disease liver disease, autoimmune disease, cardiac disease, kidney disease, cancer and gastrointestinal disease.

In a further aspect of the present disclosure, there is provided a kit for treating or preventing a disease in a subject, wherein the kit comprises a compound disclosed herein or a salt, solvate, hydrate, or prodrug thereof.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating or preventing diabetes, obesity or diabesity.

In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in improving insulin sensitivity in a subject.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for use in treating or preventing diabetes, obesity or diabesity.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for use in improving insulin sensitivity.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition disclosed herein for use in treating or preventing diabetes, obesity or diabesity.

In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition disclosed herein for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition disclosed herein for use in improving insulin sensitivity in a subject.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for use in treating or preventing diabetes, obesity or diabesity.

In another aspect of the present disclosure, there is provided a use of a pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for use in improving insulin sensitivity.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutically acceptable composition disclosed herein in the manufacture of a medicament for ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

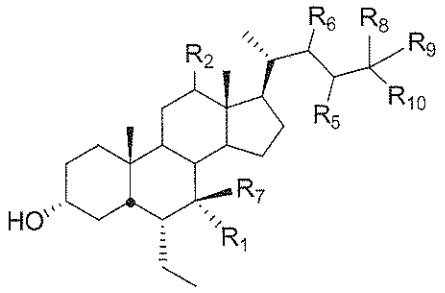
The above description sets forth rather broadly the more important features of the present present disclosure ~~invention~~ in order that the detailed description thereof that follows may be understood, and in order that the present contributions to the art may be better appreciated. Other objects and features of the present present disclosure ~~invention~~ will become apparent from the following detailed description considered in conjunction with the examples.

Brief Description of the Figures

Figure 1 is a graph that shows the impact of compound Ih3e on body weight gain in chow and high fat fed mice.

CLAIMS

1. A compound of formula III:



(III),

or a salt, hydrate, glycine or taurine amino acid conjugate, or prodrug thereof, wherein:

R_1 is hydrogen, hydroxyl, or halogen;

R_2 is hydrogen or α-hydroxyl;

R_3 is hydroxyl, $NH(CH_2)_mSO_3H$, or $NH(CH_2)_nCO_2H$;

R_5 is unsubstituted C_2-C_6 alkyl, substituted alkyl, or aryl;

R_6 is hydrogen; or

R_5 and R_6 taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms;

R_7 is hydrogen, unsubstituted or substituted alkyl, or hydroxyl;

R_8 is hydrogen, unsubstituted or substituted alkyl;

R_9 is hydrogen, unsubstituted or substituted alkyl; or

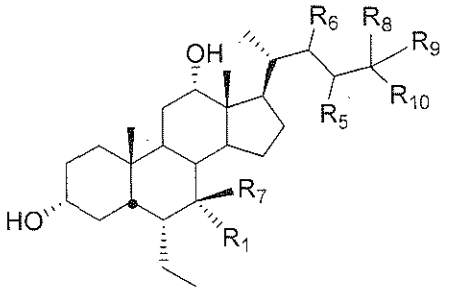
R_8 and R_9 taken together with the carbon to which they are attached form a carbonyl;

R_{10} is R_3 or SO_3H;

m is an integer 0, 1, 2, 3, 4, or 5; and

n is an integer 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, having formula IIIA:



(IIIA),

or a salt, hydrate, glycine or taurine amino acid conjugate, or prodrug thereof.

3. The compound of claim 1 or 2, wherein R_8 and R_9 taken together with the carbon to which they are attached form a carbonyl.

4. The compound of claim 3, wherein R_{10} is R_3.

5. The compound of any one of claims 1-4, wherein R_3 is selected from hydroxyl, $NH(CH_2)_2SO_3H$, and $NHCH_2CO_2H$.

6. The compound of any one of claims 1-5, wherein R_6 is hydrogen.

7. The compound of any one of claims 1-6, wherein R_5 is in the S-configuration.

8. The compound of any one of claims 1-7, wherein R_5 is unsubstituted C_2-C_6 alkyl.

9. The compound of any one of claims ~~1-7~~1-8, wherein R_5 is ~~substituted~~ methyl.

16. A kit for treating or preventing a disease in a subject, wherein the kit comprises a compound of any one of claims 1-12 or a salt, solvate, hydrate, or prodrug thereof.

17. A compound of any one of claims 1-12 for use in treating or preventing diabetes, obesity or diabesity.

18. A compound of any one of claims 1-12 for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

19. A compound of any one of claims 1-12 for use in improving insulin sensitivity in a subject.

20. Use of a compound as claimed in any one of claims 1-12, in the manufacture of a medicament for use in treating or preventing diabetes, obesity or diabesity.

21. Use of a compound as claimed in any one of claims 1-12, in the manufacture of a medicament for use in improving insulin sensitivity.

22. Use of a compound as claimed in any one of claims 1-12, in the manufacture of a medicament for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

23. A pharmaceutically acceptable composition of claim 13 for use in treating or preventing diabetes, obesity or diabesity.

24. A pharmaceutically acceptable composition of claim 13 for use in ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.

25. A pharmaceutically acceptable composition of claim 13 for use in improving insulin sensitivity in a subject.

26. Use of a pharmaceutically acceptable composition of claim 13, in the manufacture of a medicament for use in treating or preventing diabetes, obesity or diabesity.

27. Use of a pharmaceutically acceptable composition of claim 13, in the manufacture of a medicament for use in improving insulin sensitivity.

28. Use of a pharmaceutically acceptable composition of claim 13 in the manufacture of a medicament for ameliorating a metabolic disease in a subject in need thereof, wherein the metabolic disease is selected from metabolic syndrome, insulin resistance, pre-diabetic insulin resistance, hypertension, and dyslipidemia.