absorbed in the stomach. The high concentration rapidly distributes and uncouples immediately, producing high levels of heat in a short period of time. Thus, DNP has a small therapeutic index and is extremely dangerous in overdose. DNP was labelled as “extremely dangerous and not fit for human consumption” by the Federal Food, Drug and Cosmetic Act of 1938. Accordingly, there is a need for uncouplers that can safely treat mitochondria-related disorders or conditions.

[0005] 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is a novel small molecule uncoupler (Compound 1). It works as a controlled metabolic accelerator (CMA). It is designed to effectively address the root cause of metabolic diseases, the accumulation of fat and sugars in the body. CMAs work to improve cellular metabolism and increase energy expenditure and calorie consumption, reducing the accumulation of fat. Using a new controlled and targeted approach, Compound 1 can increase mitochondrial proton leak, an ongoing process in the body that dissipates energy, and accounts for 20% - 40% of daily calories. Compound 1 leverages a mitochondrial uncoupling mechanism to increase substrate utilization.

SUMMARY

[0005a] In a first aspect of the present disclosure, there is provided a use of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for weight loss or for reduction of body fat mass in a subject who has an abnormal HbA1c level.

[0006] In one example, the present disclosure provides a method for weight loss in a subject who has an abnormal HbA1c level, wherein the method comprises administering to the subject a therapeutically effective amount of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof.

[0007] In certain examples, the abnormal HbA1c level is the elevated HbA1c.

[0008] In another example, the present disclosure provides a method for reducing liver fat in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof.

[0009] In certain examples, the method result in reduction of liver fat in the subject.

[0010] In certain examples, the method is to treat non-alcoholic fatty liver disease (NAFLD) in subjects with elevated liver fat.

[0011] In certain examples, the subject has a high body mass index (BMI).

[0012] In certain examples, the reduction of liver fat in the subject is at least 30% in the subject.

[0013] In certain examples, the reduction of liver fat is least 40% in the subject with the elevated HbA1c level.

[0014] In certain examples, the methods slow the progression of non-alcoholic fatty liver disease.

[0015] In certain examples, the subject suffers from obesity, excess body fat, diabetes, high blood pressure (hypertension), dyslipidemia, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, or metabolic syndrome.

[0016] In certain examples, the subject is suffering from at least one of symptoms selected from reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling.

[0017] In certain examples, the subject suffers from disorders selected from non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0018] In certain examples, the therapeutically effective amount of Compound 1 is from about 30mg to about 1400mg per day, from about 50mg to about 100mg per day, from about 150mg to about 600mg per day, or from 200mg to 550mg orally once daily.

[0019] In certain examples, the subject experiences weight loss after administration of Compound 1, wherein weight loss is greater than 5%, 10%, 20%, or 30%.

[0020] In one example, the subject experiences at least one of:

i) a reduction of body weight by at least 5% or at least 30%;

ii) a reduction of blood pressure of at least 5 mmHg;

iii) a reduction of HbA1c by at least 0.5%, or by at least 1.5%.

[0021] In another example, the method slows the progression of obesity, hypertension, or diabetes.

DETAILED DESCRIPTION OF DRAWINGS

[0022] FIG. 1 shows the Phase 2 study design.

[0023] FIG. 2 shows the treatment effect across all doses in subjects with elevated HbA1c population.

[0024] FIG. 3 shows weight reduction in subjects with increased HbA1c.

[0025] FIG. 4 shows body fat change in subjects with elevated HbA1c population (Mean±SEM).

[0026] FIG. 5 shows weight loss in overall population and elevated HbA1c group.

CLAIMS

We claim:

1. Use of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for weight loss or for reduction of body fat mass in a subject who has an abnormal HbA1c level.

2. The use of claim 1, wherein the abnormal HbA1c level is an elevated HbA1c.

3. Use of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of non-alcoholic fatty liver disease (NAFLD) in subjects with elevated liver fat.

4. Use of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing liver fat in a subject in need thereof.

5. The use of claim 4, wherein the reduction of liver fat is at least 30% in the subject.

6. The use of claim 4 or claim 5, wherein 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at 150 mg;

optionally, wherein the use results in about 40% of liver fat reduction in the subject, or

optionally, wherein the use results in about 43% of liver fat reduction in the subject with an elevated HbA1c level.

7. The use of claim 4 or claim 5, wherein 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at 300 mg;

optionally, wherein the use results in about 70% of liver fat reduction in the subject, or

optionally, wherein the use results in about 75% of liver fat reduction in the subject with an elevated HbA1c level.

8. The use of claim 4 or claim 5, wherein 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at 450 mg;

optionally, wherein the use results in about 72% of liver fat reduction in the subject, or

optionally, wherein the use results in about 86% of liver fat reduction in the subject with an elevated HbA1c level.

9. The use of any one of claims 1-8, wherein the use slows the progression of non-alcoholic fatty liver disease.

10. The use of any one of claims 1-9, wherein the subject

(A) suffers from obesity, excess body fat, diabetes, high blood pressure (hypertension), dyslipidemia, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, or metabolic syndrome,

optionally, wherein the diabetes is type 2 diabetes (T2DM);

(B) suffers from disorders selected from non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH); and/or

(C) is suffering from at least one of symptoms selected from reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling.

11. Use of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating fibrosis, progressive fibrosis, or progressive fibrotic liver diseases NASH in a subject in need thereof.

12. The use of any one of claims 1-11, wherein the subject has high body mass index; optionally, wherein the subject has body mass index greater than 28.0 kg/m^2.

13. The use of any one of claims 1-12, wherein the subject has an elevated HbA1c level; optionally, wherein the subject has an elevated HbA1c level greater than 5.7.

14. The use of any one of claims 1-5 or 9-13, wherein 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at:

(A) from about 30mg to about 1400mg per day, from about 50mg to about 100mg per day, from about 150mg to about 600mg per day, or from 200mg to 550mg per day;

(B) about 100mg, 150mg, 200mg, 250mg, 300mg, 350mg, 400mg, 450mg, 500mg, or 600mg per day;

(C) about 150mg, 300mg, or 450mg per day; or

(D) about 30mg, 35mg, 40mg, 45mg, 50mg, 55mg, 60mg, 65mg, 70mg, 75mg, 80 mg, 85mg, 90mg, or 95mg, per day.

15. The use of any one of claims 1-5 or 9-13, wherein 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered orally once daily.

16. The use of any one of claims 1-15, wherein the subject experiences weight loss

(A) greater than 5%, 10%, 20%, 30%, or 40%; or

(B) of approximately 40%.

17. The use of claim 16, wherein:

(A) 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at about 150mg and weight loss greater than 10%;

(B) 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at about 300mg and weight loss greater than 20%; or

(C) 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered at about 450mg and weight loss greater than 30%.

18. The use of any one of claims 1-4, wherein the subject experiences at least one of:

i) a reduction of body weight by at least 5% or at least 30%;

ii) a reduction of blood pressure of at least 5 mmHg;

iii) a reduction of HbA1c at least 0.5%;

iv) a reduction of lipids by at least 10%; and/or

v) a reduction of liver fat by at least 30%.

19. The use of claim 18, wherein the subject experiences a reduction of HbA1c greater than 1.5%.

20. The use of any one of claims 1-19, wherein the use slows the progression of obesity, hypertension, or diabetes.