[0004] The administration of chemical uncouplers of mitochondria as a means to decrease fat deposits has been a scientific goal for many years. While there are several small molecules which uncouple mitochondrial oxidative phosphorylation, the most well-known is 2,4-dinitrophenol (DNP). Though DNP is known to uncouple with robust effect, it unfortunately is associated with an unacceptable high rate of significant adverse effects (*J. Med. Toxicol.* 2011 Sep; 7(3): 205-212). These adverse effects may include hyperthermia, tachycardia, diaphoresis and tachypnoea, eventually leading to death. Being a small, highly permeable, lipophilic acid, DNP is rapidly 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.

[0006] Compound 1 has been studied with nonclinical models. The demonstration of potent therapeutic activity in relevant rodent models of disease, together with the pharmacokinetics and safety profile, support that Compound 1 can be used beneficially and safely for treating a wide range of mitochondria-related diseases. It was also discovered that Compound 1 may be efficacious in treating cardiovascular diseases.

SUMMARY

[0006a] 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 reducing a cardiovascular risk or mortality in a subject suffering from a symptom due to a cardiovascular disease.

[0006b] In another 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 treating HFpEF, HFrEF, or HFmrEF in a subject.

[0006c] In yet another 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 reducing blood pressure in a subject; optionally, wherein the reducing blood pressure comprises reducing diastolic blood pressure and/or reducing systolic blood pressure;

optionally, wherein the medicament is to be administered to the subject, and wherein the use reduces or slows the progression of the risk of developing a cardiovascular disease or heart failure.

[0006d] In a further 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 treating mitochondria-related disorders or conditions without causing a clinically significant risk of adverse events in a subject.

[0006e] In another 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 reducing toxicity or side effects, or preventing overdose, in treating mitochondria-related disorders or conditions in a subject;

optionally, wherein the overdose is associated with a mitochondria uncoupler; and

optionally, wherein the mitochondria uncoupler is 2,4-dinitrophenol.

[0006f] In yet another 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 increasing metabolic rate without causing a clinically significant risk of adverse events in a subject;

optionally, wherein the resting metabolic rate is increased by at least 10% or by at least 20%.

[0006g] In a further 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 increase resting energy expenditure in a subject;

optionally, wherein the medicament is to be administered to the subject, and wherein the subject experiences an increase of resting energy expenditure of at least 10%, at least 20%, or at least 30% after the administration.

[0006h] In another 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 treating dysmetabolism in a subject;

optionally, wherein the subject suffers from at least one of: increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.

[0006i] In yet another 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 treating severe hypertriglyceridemia or hypertriglyceridemia associated with cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease in a subject.

[0006j] In a further 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 reducing liver fat by at least 50% or reducing lipids by at least 10% in a subject.

[0006k] In another 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 treating a cardiovascular disease, obesity, excess body fat, type 2 diabetes, insulin resistance or intolerance, high blood pressure, dyslipidemia, atherosclerosis, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, metabolic syndrome, Rett's syndrome, metabolic syndrome associated with aging, metabolic diseases associated with increased reactive oxygen species (ROS), Friedreich's ataxia, NAFLD, NASH, noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, cancer, or hepatocellular carcinoma, to the use achieving at least one of:

i) a steady state of maximum plasma concentration (C_{max}) of 2,4-dinitrophenol from about 80 ng/mL to about 8300 ng/mL;

ii) mean half-life ($t_{1/2}$) of 2,4-dinitrophenol about 20-50 hours, about 25-40 hours, or about 30-40 hours;

iii) median time to maximum plasma concentration (T_{max}) of 2,4-dinitrophenol about 6-8 hours or about 6-10 hours;

iv) median area under the curve extrapolated to infinity (AUC_{inf}) of 2,4-dinitrophenol about 3 h*µg/mL to about 420 h*µg/mL; and

v) AUC/C_{max} ratio of about 18.

[0007] In some examples, the present disclosure provides a method for treating a cardiovascular disease in a subject comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0008] In some examples, the present disclosure provides a method of treating heart failure, comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0009] In some examples, the present disclosure provides a method of reducing a cardiovascular risk or mortality in a subject suffering from a symptom due to a cardiovascular disease, comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0010] In some examples, the cardiovascular disease is selected from the group consisting of heart failure, heart attack, coronary artery disease, and coronary heart disease (CHD).

[0011] Heart failure as used herein includes heart failure with preserved ejection fraction (HFpEF), or heart failure with reduced ejection fraction (HFrEF), or heart failure with mid-range ejection fraction (HFmrEF).

[0012] In some examples, the cardiovascular disease is HFpEF.

[0013] In some examples, the cardiovascular disease is HFrEF.

[0014] In some examples, the cardiovascular disease is HFmrEF.

[0015] In some examples, the present disclosure provides a method for treating heart failure with preserved ejection fraction (HFpEF) in a subject, 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.

[0016] In some examples, the present disclosure provides a method for treating heart failure with reduced ejection fraction (HFrEF) in a subject, 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.

[0017] In some examples, the present disclosure provides a method for treating heart failure with mid-range ejection fraction (HFmrEF) in a subject, 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.

[0018] In some examples, the subject is suffering from at least one of shortness of breath, shortness of breath with exertion, impaired energetics in the heart, dizziness, fatigue, dyspnea, palpitations (atrial fibrillation), chest discomfort, edema, syncope, and a limit on an activity of daily living.

[0019] In some examples, the limit on an activity of daily living is difficulties on personal care, mobility, and eating.

[0020] In some examples, the subject is suffering from symptoms selected from reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling.

[0021] In some examples, the subject is suffering from at least one of coronary artery disease, hypertension, and heart murmur.

[0022] In some examples, the present disclosure provides a method of reducing blood pressure in a subject comprising administering to the subject a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0023] In some examples, the subject is suffering from at least one of cardiovascular disease, hypertension, resistant hypertension, and severe hypertension.

[0024] In some examples, the cardiovascular disease is heart failure (which may be HFpEF, HFrEF, or HFmrEF), heart attack, coronary artery disease, or coronary heart disease (CHD).

[0025] In some examples, the subject has hypertension associated with HFpEF.

[0026] In some examples, the subject has hypertension associated with HFrEF.

[0027] In some examples, the subject has hypertension associated with HFmrEF.

[0028] In some examples, wherein the subject experiences a reduction of blood pressure of at least 5 mmHg after the administration.

[0029] In some examples, the method reduces the risk of developing a cardiovascular disease, and/or reduces the risk of HFpEF, HFrEF, or HFmrEF.

[0030] In some examples, the method slows the progression of HFpEF, HFrEF, or HFmrEF.

[0031] In some examples, the method comprises at least one of:

i) extending the half-life ($t_{1/2}$) of DNP;

ii) delaying the time to maximum plasma concentration (T_{max}) of DNP;

iii) lowering maximum plasma concentration (C_{max}) of DNP; and

iv) increasing area under the curve (AUC).

[0032] In some examples, the subject does not experience significant systemic toxicity, side effects, significant increase in body temperature, or significant increase in heart rate after administration.

[0033] In some examples, the present disclosure provides a method of treating a cardiovascular disease by achieving:

i) asteady state of maximum plasma concentration (C_{max}) of DNP from about 80 ng/mL to about 8300 ng/mL;

ii) mean half-life ($t_{1/2}$) of DNP about 20-50 hours, about 25-40 hours, or about 30-40 hours;

iii) median time to maximum plasma concentration (T_{max}) of DNP about 6-8 hours or about 6-10 hours;

iv) median area under the curve extrapolated to infinity (AUC_{inf}) of DNP about 3 h*µg/mL to about 420 h*µg/mL; and

AUC/C_{max} ratio of about 18,

by administering to a subject about 30mg to about 1400mg of Compound 1 or a pharmaceutically acceptable salt thereof.

[0034] In some examples, the present disclosure provides a method of treating mitochondria-related disorders or conditions without causing a clinically significant risk of adverse events in a subject, the method comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0035] In some examples, the present disclosure provides a method of reducing toxicity or side effects in treating mitochondria-related disorders or conditions in a subject, comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0036] In some examples, the present disclosure provides a method of preventing overdose in treating mitochondria-related disorders or conditions in a subject, comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0037] In some examples, the present disclosure provides a method for increasing metabolic rate or resting energy expenditure without causing a clinically significant risk of adverse events in a subject, comprising administering to the subject a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0038] In some examples, the present disclosure provides a method for treating dysmetabolism in a subject comprising administering to the subject a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0039] In some examples, the present disclosure provides a method of treating hypertriglyceridemia associated with cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease in a subject, comprising administering to the subject a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0040] In some examples, the present disclosure provides a method of treating severe hypertriglyceridemia in a subject, comprising administering to the subject a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0041] In some examples, the present disclosure provides a method of reducing liver fat by at least 50% or a method of reducing lipids by at least 10% in a subject, the method comprising administering to the subject a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0042] In some examples, the present disclosure provides a method of treating obesity, excess body fat, type 2 diabetes, insulin resistance or intolerance, high blood pressure, dyslipidemia, atherosclerosis, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, metabolic syndrome, Rett's syndrome, metabolic syndrome associated with aging, metabolic diseases associated with increased reactive oxygen species (ROS), Friedreich's ataxia, NAFLD, NASH, noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, or hepatocellular carcinoma, the method comprising administering a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof in a subject, to achieve at least one of:

i) a steady state of maximum plasma concentration (C_{max}) of 2,4-dinitrophenol from about 80 ng/mL to about 8300 ng/mL;

ii) mean half-life ($t_{1/2}$) of 2,4-dinitrophenol about 20-50 hours, about 25-40 hours, or about 30-40 hours;

iii) median time to maximum plasma concentration (T_{max}) of 2,4-dinitrophenol about 6-8 hours or about 6-10 hours;

iv) median area under the curve extrapolated to infinity (AUC_{inf}) of 2,4-dinitrophenol about 3 h*µg/mL to about 420 h*µg/mL; and

v) AUC/C_{max} ratio of about 18.

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 reducing a cardiovascular risk or mortality in a subject suffering from a symptom due to a cardiovascular disease.

2. The use of claim 1, wherein:

A) the symptom is shortness of breath, shortness of breath with exertion, dizziness, chest pain, syncope, fatigue, impaired energetics in the heart, or limits on activities of daily living;

optionally, wherein the limit on an activity of daily living is difficulties on personal care, mobility, or eating; or

B) the cardiovascular disease comprises heart failure, heart attack, coronary artery disease, or coronary heart disease (CHD);

optionally, wherein heart failure comprises heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), or heart failure with mid-range ejection fraction (HFmrEF).

3. The use of claim 1 or claim 2, wherein the medicament is to be administered to the subject, and wherein the subject experiences a reduction in the risk of a major cardiovascular event after administration; optionally, wherein the major cardiovascular event is death or hospitalization for worsening of the disease.

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 treating HFpEF, HFrEF, or HFmrEF in a subject.

5. The use of claim 4, wherein the subject is suffering:

A) from at least one of the symptoms selected from shortness of breath, shortness of breath with exertion, impaired energetics in the heart, dizziness, fatigue, dyspnea, palpitations (atrial fibrillation), chest discomfort, edema, syncope, and a limit on an activity of daily living;

optionally, wherein the limit on an activity of daily living is difficulties on personal care, mobility, and eating;

B) from at least one of symptoms selected from reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling; or

C) from at least one of symptoms selected from coronary artery disease, hypertension, and heart murmur.

6. The use of claim 1 or 4, wherein the medicament is to be administered to the subject, and wherein:

A) the subject experiences an improvement of cardiac bioenergetic deficiency after administration, wherein the improvement comprising: a) weight loss > 5%, b) reduction in blood pressure, and/or c) a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infraction;

B) the use increases VO_2 in the subject after administration; or

C) the use increases 6-minute walk distance (6MWD) after the administration.

7. The use of claim 1 or 4, wherein the medicament is to be administered to the subject, and wherein the use further comprising:

A) assessing peak oxygen consumption (VO_2) and/or VE/CO_2 or VE/VCO_2 slope in the subject during exercise before and after administration of the therapeutically effective amount of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, wherein an increase in VO_2 in the subject after administration indicates a reduction in the extent of HFpEF, HFrEF, HFmrEF or one or more symptomatic components or conditions of cardiovascular disease thereof in the subject;

B) assessing 6-minute walk distance (6MWD) in the subject during exercise before and after administration of the therapeutically effective amount of 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, wherein an increase in 6MWD in the subject after administration indicates a reduction in the extent of HFpEF or the at least one symptomatic component or condition thereof in the subject; or

C) assessing a NYHA classification score of the subject before and after administration; optionally:

C.1) wherein a decreased NYHA score after administration indicates a reduction in the extent of the cardiac disease in the subject; or

C.2) wherein the use decreases the NYHA classification score of the subject after administration from Class III to Class II, or from Class II to Class I.

8. 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 blood pressure in a subject; optionally, wherein the reducing blood pressure comprises reducing diastolic blood pressure and/or reducing systolic blood pressure;

optionally, wherein the medicament is to be administered to the subject, and wherein the use reduces or slows the progression of the risk of developing a cardiovascular disease or heart failure.

9. The use of claim 8, wherein the medicament is to be administered to the subject, and wherein the subject:

A) is suffering from cardiovascular disease, hypertension, resistant hypertension, or severe hypertension;

optionally, wherein the cardiovascular disease comprises heart failure, heart attack, coronary artery disease, or coronary heart disease (CHD); and

optionally, wherein heart failure comprises HFpEF, HFrEF, or HFmrEF;

B) has hypertension associated with HFpEF, HFrEF, or HFmrEF;

C) is suffering from at least one of symptoms selected from headaches, shortness of breath, chest pain, nosebleeds, dizziness, fatigue, vision problem, irregular heartbeat, blood in urine, sweating, trouble sleeping, and blood spots in eyes; or

D) experiences a reduction of blood pressure of at least 5 mmHg after administration.

10. The use of any one of claims 1, 4, or 8, wherein the subject suffers from obesity, excess body fat, diabetes, high blood pressure (hypertension), dyslipidemia, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, or metabolic syndrome.

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 mitochondria-related disorders or conditions without causing a clinically significant risk of adverse events in a subject.

12. 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 toxicity or side effects, or preventing overdose, in treating mitochondria-related disorders or conditions in a subject;

optionally, wherein the overdose is associated with a mitochondria uncoupler; and

optionally, wherein the mitochondria uncoupler is 2,4-dinitrophenol.

13. The use of claim 12, comprising at least one of:

i) extending the half-life ($t_{1/2}$) of 2,4-dinitrophenol;

ii) delaying the time to maximum plasma concentration (T_{max}) of 2,4-dinitrophenol;

iii) lowering maximum plasma concentration (C_{max}) of 2,4-dinitrophenol; and

iv) increasing the area under the curve (AUC).

14. The use of any one of claims 11-13, wherein:

A) the disorder is obesity, excess body fat, diabetes, insulin resistance or intolerance, high blood pressure, dyslipidemia, cardiovascular diseases, atherosclerosis, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, metabolic syndrome, Rett's syndrome, metabolic syndrome associated with aging, metabolic diseases associated with increased reactive oxygen species (ROS), Friedreich's ataxia, or liver diseases;

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

B) the cardiovascular diseases comprise heart failure, HFpEF, HFrEF, HFmrEF, heart attack, coronary artery disease, or CHD;

C) the liver diseases comprise non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, or hepatocellular carcinoma; or

D) the condition is at least one of steatosis, inflammation, fibrosis, cirrhosis, and hepatocyte injury in NASH.

15. The use of claim 11 or claim 14, wherein the medicament is to be administered to the subject, and wherein the use provides at least one of the following in the subject after administration:

i) a steady state of maximum plasma concentration (C_{max}) of 2,4-dinitrophenol from about 80 ng/mL to about 8300 ng/mL;

ii) mean half-life ($t_{1/2}$) of 2,4-dinitrophenol about 20-50 hours, about 25-40 hours, or about 30-40 hours;

iii) median time to maximum plasma concentration (T_{max}) of 2,4-dinitrophenol about 6-8 hours or about 6-10 hours;

iv) median area under the curve extrapolated to infinity (AUC_{inf}) of 2,4-dinitrophenol about 3 h*µg/mL to about 420 h*µg/mL; and

v) AUC/C_{max} ratio of about 18.

16. 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 increasing metabolic rate without causing a clinically significant risk of adverse events in a subject;

optionally, wherein the resting metabolic rate is increased by at least 10% or by at least 20%.

17. 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 increase resting energy expenditure in a subject;

optionally, wherein the medicament is to be administered to the subject, and wherein the subject experiences an increase of resting energy expenditure of at least 10%, at least 20%, or at least 30% after the administration.

18. 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 dysmetabolism in a subject;

optionally, wherein the subject suffers from at least one of: increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.

19. The use of any one of claims 1-18, wherein the medicament is to be administered to the subject, and wherein the subject experiences a reduction in at least one of body weight, blood pressure, and blood glucose after the administration;

optionally, wherein the subject experiences at least one of:

i) a reduction of body weight by at least 5% or at least 10%;

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

iii) a reduction of HbA_{1c} by at least 0.5%, or at least 1.5%;

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

v) a reduction of liver fat by at least 50%.

20. The use of any one of claims 11-19, wherein the use slows the progression of at least one of: atherosclerosis, NAFLD, NASH, noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma; or

wherein the use accelerates human body's natural processes to improve cardio-metabolic processes.

21. 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 severe hypertriglyceridemia or hypertriglyceridemia associated with cardiovascular disease,

atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease in a subject.

22. The use of claim 21, wherein:

A) the cardiovascular disease comprises heart failure, HFpEF, HFrEF, HFmrEF, heart attack, coronary artery disease, or CHD;

B) the liver diseases comprise non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, or hepatocellular carcinoma;

C) the subject is suffering from at least one of abdominal pain, pain in the mid-epigastric, chest, or back regions, gastrointestinal pain, difficulty breathing, loss of appetite, nausea, vomiting, inflammation of the pancreas, memory loss, dementia, xanthelasmas, corneal arcus, and xanthomas; or

D) the subject has moderate hypertriglyceridemia associated with cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease; or severe hypertriglyceridemia associated with cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease.

23. The use of claim 21, wherein:

(I) the use is for treating severe hypertriglyceridemia, and wherein the subject:

A) is suffering from at least one of abdominal pain, pain in the mid-epigastric, chest, or back regions, gastrointestinal pain, difficulty breathing, loss of appetite, nausea, vomiting, inflammation of the pancreas, memory loss, dementia, xanthelasmas, corneal arcus, and xanthomas;

B) has a triglyceride blood level above 500 mg/dL;

C) has treatment resistant severe hypertriglyceridemia; or

D) has severe hypertriglyceridemia associated with cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease; or

(II) wherein the medicament is to be administered to the subject, and wherein the use:

A) comprises lowering low-density lipoprotein cholesterol levels and/or lowering non–high-density lipoprotein cholesterol levels;

B) comprises at least one of:

i) lowering triglyceride levels by at least 5%, at least 10%, or at least 20%;

ii) lowering low-density lipoprotein cholesterol levels by at least 5%, at least 10%, or at least 20%; and

iii) lowering non–high-density lipoprotein cholesterol levels by at least 5%, at least 10%, or at least 20%; or

C) slows the progression of at least one of the cardiovascular disease, atherosclerosis, obesity, hypertension, diabetes, insulin resistance, and/or liver disease; and/or reduces the risk of a major cardiovascular event after the administration; optionally, wherein the major cardiovascular event is death or hospitalization for worsening of the disease.

24. 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 by at least 50% or reducing lipids by at least 10% in a subject.

25. The use of claim 24, wherein the subject suffers from at least one of obesity, excess body fat, type 2 diabetes, insulin resistance or intolerance, high blood pressure, dyslipidemia, atherosclerosis, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, metabolic syndrome, Rett's syndrome, metabolic syndrome associated with aging, metabolic diseases associated with increased reactive oxygen species (ROS), Friedreich's ataxia, NAFLD, NASH, noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma.

26. The use of claim 24 or claim 25, wherein the use provides at least one of:

i) a reduction of body weight by at least 10%;

ii) a reduction of HbA_{1c} by at least 0.5%, or at least 1.5%;

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

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

v) a reduction of liver fat by at least 50%;

vi) a reduction of serum alanine aminotransferase (ALT); and

vii) a reduction of aspartate aminotransferase (AST).

27. The use of any one of claims 1-26, wherein the medicament is to be administered to the subject, and wherein the use does not cause a clinically significant risk of adverse events in the subject after administration; optionally,

A) wherein the adverse events comprise at least one of nausea, vomiting, sweating, dizziness, headaches, cataracts, glaucoma, pyrexia, hyperthermia, tachycardia, diaphoresis, tachypnoea, and death;

B) wherein the adverse event is characterized by at least one of elevated body temperature, elevated heart rate, abnormal sweating, erythema, perspiration, dehydration, and abnormally rapid breathing;

C) wherein the adverse event is associated with cardiovascular collapse, cardiac arrest, and/or death; or

D) wherein the adverse event is associated with cardiac arrest; and

optionally, wherein the adverse events are associated with a mitochondria uncoupler; optionally, wherein the mitochondria uncoupler is 2,4-dinitrophenol.

28. 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 a cardiovascular disease, obesity, excess body fat, type 2 diabetes, insulin resistance or intolerance, high blood pressure, dyslipidemia, atherosclerosis, hypertriglyceridemia, acquired lipodystrophy, inherited lipodystrophy, partial lipodystrophy, metabolic syndrome, Rett's syndrome, metabolic syndrome associated with aging, metabolic diseases associated with increased reactive oxygen species (ROS), Friedreich's ataxia, NAFLD, NASH, noncirrhotic NASH, noncirrhotic NASH with liver fibrosis, hepatic steatosis, hepatic fibrosis, liver cirrhosis, cancer, or hepatocellular carcinoma, to the use achieving at least one of:

i) a steady state of maximum plasma concentration (C_{max}) of 2,4-dinitrophenol from about 80 ng/mL to about 8300 ng/mL;

ii) mean half-life ($t_{1/2}$) of 2,4-dinitrophenol about 20-50 hours, about 25-40 hours, or about 30-40 hours;

iii) median time to maximum plasma concentration (T_{max}) of 2,4-dinitrophenol about 6-8 hours or about 6-10 hours;

iv) median area under the curve extrapolated to infinity (AUC_{inf}) of 2,4-dinitrophenol about 3 h*µg/mL to about 420 h*µg/mL; and

v) AUC/C_{max} ratio of about 18.

29. The use of any one of claims 1-28, wherein the medicament is to be administered to the subject, and wherein the subject:

A) has elevated Body Mass Index (BMI);

optionally, wherein the subject has BMI of about 28.0 kg/m^2 to about 45.0 kg/m^2; and/or

B.1) is in a fasted condition before administration; or

B.2) is in a fed condition before administration.

30. The use of any one of claims 1-29, wherein the 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount of:

A) from about 30mg to about 1400mg per day, from about 100mg to about 1000mg per day, from about 150mg to about 600mg per day, or from 200mg to 550mg per day;

B) about 30mg, 50mg, 75mg, 100mg, 150mg, 170mg, 200mg, 250mg, 300mg, 340mg, 350mg, 400mg, 450mg, 500mg, 510mg, 550mg, 600mg, 650mg, 700mg, 750mg, 800mg, 850mg, 900mg, 950mg, 1000mg, 1050mg, 1100mg, 1150mg, 1200mg, 1250mg, 1300mg, 1350mg, or 1400mg per day;

C) about 30mg, 100mg, 200mg, 500mg, 600mg, 1050mg, or 1400mg per day;

D) about 200mg, 400mg, or 550mg per day;

E) about 170mg, 340mg, 510mg per day; or

F) about 150mg, 300mg, 450mg per day;

optionally, wherein the medicament comprising 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered orally once daily; and/or

optionally, wherein the medicament comprising 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered once daily for two weeks, four weeks, six weeks, eight weeks, ten weeks, one month, two months, three months, four months, six months, eight month, or one year.