[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 one aspect, the present disclosure provides 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.

[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.

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 blood pressure in a subject.

2. The use of claim 1, wherein the reducing blood pressure comprises reducing diastolic blood pressure and/or reducing systolic blood pressure.

3. The use of claim 1, wherein the use reduces or slows the progression of the risk of developing a cardiovascular disease or heart failure.

4. The use of any one of claims 1-3, wherein the medicament is to be administered to the subject, and wherein the subject:

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.

5. The use of any one of claims 1-3, wherein the medicament is to be administered to the subject, and wherein the subject has hypertension associated with HFpEF, HFrEF, or HFmrEF.

6. The use of any one of claims 1-3, wherein the medicament is to be administered to the subject, and wherein the subject 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.

7. The use of any one of claims 1-3, wherein the medicament is to be administered to the subject, and wherein the subject experiences a reduction of blood pressure of at least 5 mmHg after administration.

8. The use of any one of claims 1-7, 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.

9. The use of any one of claims 1-8, wherein the medicament is to be administered to the subject, and wherein the subject experiences a reduction in at least one of body weight or blood glucose after the administration.

10. The use of claim 9, 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 HbA_{1c} by at least 0.5%, or at least 1.5%;

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

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

11. The use of claim 9 or 10, 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.

12. The use of any one of claims 1-11, 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.

13. The use of claim 12,

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.

14. The use of claim 13, wherein the use does not cause a clinically significant risk of adverse events after administration, wherein the adverse events are associated with a mitochondria uncoupler;

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

15. The use of any one of claims 1-14, wherein the medicament is to be administered to the subject, and wherein the subject has elevated Body Mass Index (BMI);

optionally, wherein the subject has BMI of 28.0 kg/m^2 to 45.0 kg/m^2.

16. The use of any one of claims 1-15, wherein the medicament is to be administered to the subject, and wherein the subject:

A) is in a fasted condition before administration; or

B) is in a fed condition before administration.

17. The use of any one of claims 1-16, 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 30mg to 1400mg per day, from 100mg to 1000mg per day, from 150mg to 600mg per day, or from 200mg to 550mg per day;

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

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

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

F) 150mg, 300mg, 450mg per day.

18. The use of any one of claims 1-17, wherein the medicament comprising 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitro-1H-imidazole is to be administered orally once daily.

19. The use of any one of claims 1-18, 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.