effective drugs to induce weight loss has been a major research goal for decades. However, to date the drugs that have shown efficacy have been burdened with significant side effects or have shown only modest efficacy. For example, amphetamines have been used effectively as appetite suppressants but have a strong risk of dependence along with other side effects. The discovery of leptin, a peptide hormone that plays a major role in appetite regulation, was considered to be a potential breakthrough in the treatment of obesity, but in clinical trials, leptin was not effective. More recently, cannabinoid receptor antagonists were under development as anti-obesity drugs but showed unacceptable psychiatric side effects. Similarly, drugs designed to reduce fat absorption in the digestive tract have been associated with significant gastrointestinal side effects.

Accordingly, there is a significant need for new anti-obesity treatments. In particular, there is a need for anti-obesity treatments with limited side effects that may be safely used in combination with other drugs that are in common use in obese patients, such as antidiabetic drugs, antihypertensive drugs, cholesterol-reducing agents, and insulin. Thus, agents that can be used for the treatment of obesity would represent a significant advance.

SUMMARY

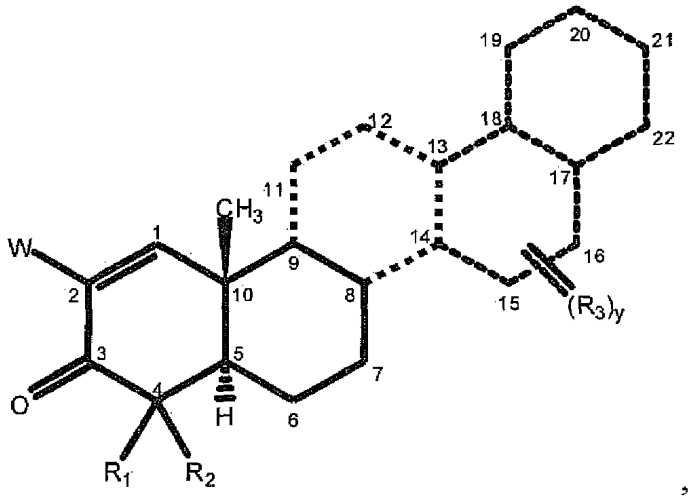
Thus, there are disclosed methods of treating overweight or obese subjects with selective activators of the antioxidant transcription factor Nrf2, such as an antioxidant inflammation modulator (AIM) so as to reduce the weight of the subject. In some examples, there is described a method of reducing weight in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the subject's weight. In some examples, there is described a method of pt in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the subject's weight.

In some examples, the subject has excess body fat. In some examples, the subject is overweight. In some examples, the subject's body mass index (BMI) is from 25 kg/m^2 to 30 kg/m^2. In some examples, the subject is obese or exhibits one of more symptoms of obesity. In some examples, the obesity is class I. In some examples, the subject's BMI is from 30 kg/m^2 to 35 kg/m^2. In some examples, the obesity is class II. In some examples, the subject's BMI is from 35 kg/m^2 to 40 kg/m^2. In some

examples, the obesity is class III. In some examples, the subject's BMI is from 40 kg/m^2 to 80 kg/m^2. In some examples, the subject is a human subject.

In some variations of one or more of the above examples, the method reduces a subject's weight by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45% 50%, 55%, 60% or 65%. In some variations of one or more of the above examples, the method also selectively induces Nrf2 in the subject. In some variations of one or more of the above examples, the method also inhibits activation of NF-κB in the subject.

In some variations of one or more of the above examples, the AIM is a compound of the formula:



wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq 8)}$, substituted alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, substituted alkenyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$ or substituted alkoxy$_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenylaminooxydiyl$_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylidene$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$,

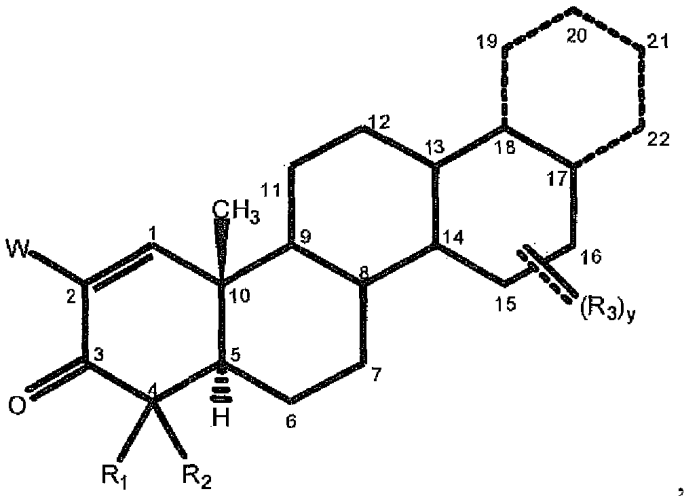
alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkoxyamino$_{(C\leq12)}$, alkenylamino$_{(C\leq12)}$, alkynylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, heteroaralkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenyl-aminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above examples, the AIM is a compound of the formula:



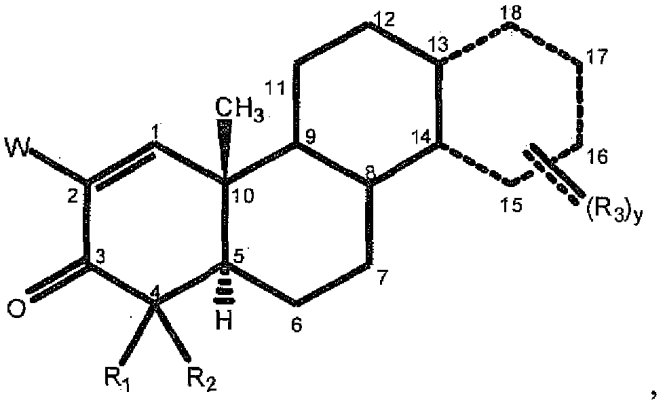
wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

In some variations of one or more of the above examples, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

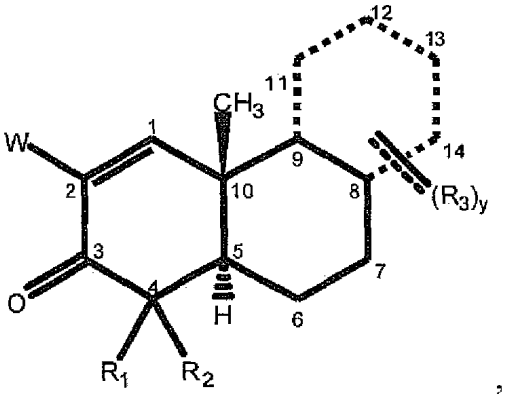
$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkoxyamino_{(C\leq 12)}$, $alkenylamino_{(C\leq 12)}$, $alkynylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $heteroaralkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, $alkylimino_{(C\leq 12)}$, $alkenylimino_{(C\leq 12)}$, $alkynylimino_{(C\leq 12)}$, $arylimino_{(C\leq 12)}$, $aralkylimino_{(C\leq 12)}$, $heteroarylimino_{(C\leq 12)}$, $heteroaralkylimino_{(C\leq 12)}$, $acylimino_{(C\leq 12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenyl-aminooxydiyl$_{(C\leq 18)}$; and

y is from 0 to 7;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some examples, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq 8)}$, substituted alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, substituted alkenyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$ or substituted alkoxy$_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenylaminooxydiyl$_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylidene$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, alkenyloxy$_{(C\leq 12)}$, alkynyloxy$_{(C\leq 12)}$, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, heteroaryloxy$_{(C\leq 12)}$, heteroaralkoxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, alkoxyamino$_{(C\leq 12)}$, alkenylamino$_{(C\leq 12)}$, alkynylamino$_{(C\leq 12)}$, arylamino$_{(C\leq 12)}$, aralkyl-amino$_{(C\leq 12)}$, heteroarylamino$_{(C\leq 12)}$, heteroaralkylamino$_{(C\leq 12)}$, alkyl-

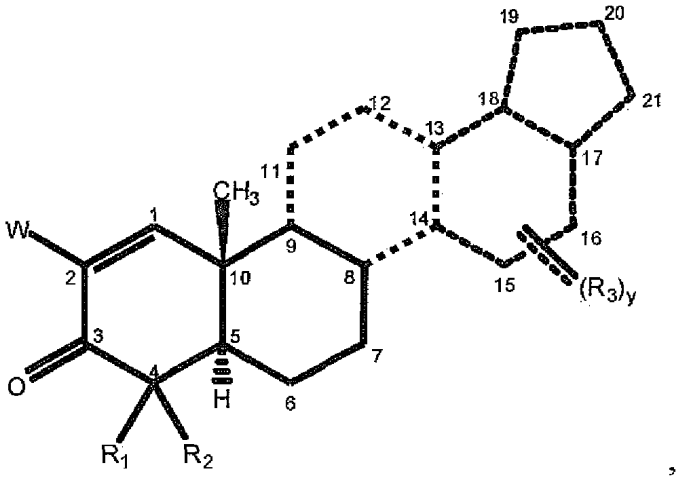
sulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenyl-aminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 6;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above examples, the AIM is a compound of the formula:



wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkylidene_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylimino_{(C\leq12)}$, $alkenylimino_{(C\leq12)}$, $alkynylimino_{(C\leq12)}$, $arylimino_{(C\leq12)}$, $aralkylimino_{(C\leq12)}$, $heteroarylimino_{(C\leq12)}$, $heteroaralkylimino_{(C\leq12)}$, $acylimino_{(C\leq12)}$ or a substituted version of any of these groups; or

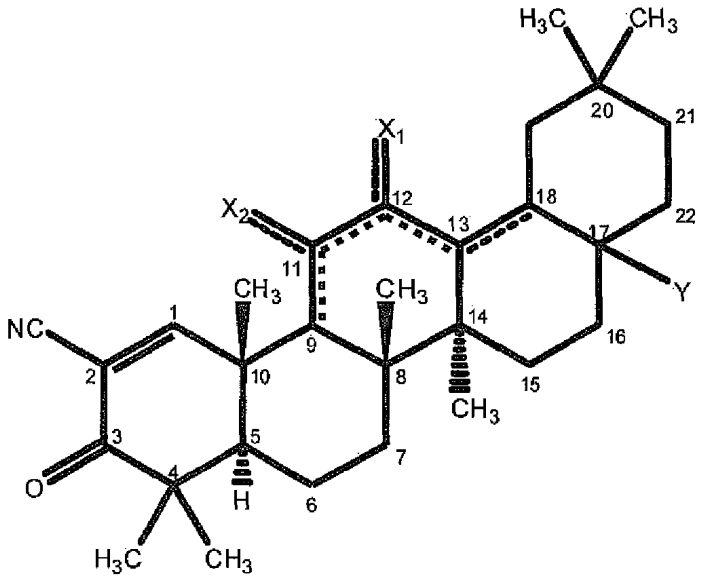
any two R_3 in $(R_3)_y$ are taken together and are $alkanediyl_{(C\leq18)}$, $alkenediyl_{(C\leq18)}$, $arenediyl_{(C\leq18)}$, $alkoxydiyl_{(C\leq18)}$, $alkenyloxydiyl_{(C\leq18)}$, $alkylaminodiyl_{(C\leq18)}$, $alkenylaminodiyl_{(C\leq18)}$, or $alkenylaminooxydiyl_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above examples, W is cyano, fluoro or $-CF_3$.

In some variations of one or more of the above examples, the AIM is a compound of the formula:



wherein:

X_1 and X_2 are independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkylidene_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylimino_{(C\leq12)}$, $alkenylimino_{(C\leq12)}$, $alkynylimino_{(C\leq12)}$, $arylimino_{(C\leq12)}$, $aralkylimino_{(C\leq12)}$, $heteroarylimino_{(C\leq12)}$, $heteroaralkylimino_{(C\leq12)}$, $acylimino_{(C\leq12)}$ or a substituted version of any of these groups;

Y is hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, mercapto, $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$ or $alkylsulfonylamino_{(C\leq12)}$; and

or a pharmaceutically-acceptable salt or tautomer thereof.

In some examples, the AIM is bardoxolone methyl. In some of the examples, at least a portion of the bardoxolone methyl is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. For example, the X-ray diffraction pattern (CuKα) is in some examples substantially as shown in FIG. 1A or FIG. 1B. In some of the examples, at least a portion of the bardoxolone methyl is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g. In some of the examples, the T_g value is in the range of about

120 °C to about 135 °C. In some of the examples, the T_g value is in the range of about 125 °C to about 130 °C.

In some variations of one or more of the above examples, the sufficient amount to reduce the subject's weight is a daily dose from about 0.1 mg to about 30 mg of the AIM.

In some variations of one or more of the above examples, the AIM is administered orally, intraarterially or intravenously. In some variations of one or more of the above examples, the AIM is formulated as a hard or soft capsule or a tablet. In some variations of one or more of the above examples, the AIM is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient, for example, the excipient may be a methacrylic acid – ethyl acrylate copolymer. In some examples, the ratio of the methacrylic acid – ethyl acrylate copolymer is 1:1.

In some variations of one or more of the above examples, the weight of the subject has been measured or will be measured. For example, in some examples, the weight of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

In some variations of one or more of the above examples, the BMI of the subject has been measured or will be measured. For example, in some examples, the BMI of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

In some variations of one or more of the above examples, the subject also suffers from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer, or has undergone or will undergo organ or tissue transplant.

In some variations of one or more of the above examples, the subject does not also suffer from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer, or has not or will not undergo transplant.

In some variations of one or more of the above examples, the subject has diabetes. In some variations of one or more of the above examples, the subject does not have diabetes. In some variations of one or more of the above examples, the subject exhibits one or more symptoms of diabetes. In some variations of one or more of the above examples, the subject does not exhibit any symptoms of diabetes. In some variations of one or more of the above examples, the subject has been identified as having diabetes. In some variations of one or more of the above examples, the subject has been identified as

not having diabetes. In some variations of one or more of the above examples, the level of a marker of diabetes in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the subject has elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some variations of one or more of the above examples, the subject does not have elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some variations of one or more of the above examples, the subject does not have elevated levels of any biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some examples, the biomarker is a marker of insulin resistance, leptin resistance, adiponectin resistance, cardiovascular stress, or renal dysfunction. In some examples, the biomarker is a marker of insulin resistance. In some examples, the biomarker is fasting glucose or hemoglobin A1c. In some examples, the biomarker is a marker of leptin resistance. In some examples, the biomarker is a marker of adiponectin resistance. In some examples, the biomarker is adiponectin. In some examples, the biomarker is a marker of cardiovascular stress. In some examples, the biomarker is circulating endothelial cells or C-reactive protein. In some examples, the biomarker is circulating endothelial cells. In some examples, the biomarker is iNOS-positive circulating endothelial cells. In some examples, the biomarker is a marker of renal disease. In some examples, the biomarker is serum creatinine. In some examples, the biomarker is cystatin C. In some examples, the biomarker is uric acid.

In some variations of one or more of the above examples, the subject has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD. In some variations of one or more of the above examples, the subject does not have chronic kidney disease (CKD). In some variations of one or more of the above examples, the subject does not exhibit any symptoms of CKD. In some variations of one or more of the above examples, the subject has been identified as having CKD. In some variations of one or more of the above examples, the subject has been identified as not having CKD. In some variations of one or more of the above examples, the level of a marker of CKD in the subject has been measured or will be measured. In some of the examples, the CKD is characterized by a serum creatinine level of 1.3-3.0 mg/DL where the subject is a human female or a serum creatinine level of 1.5-3.0 mg/DL where the subject is a human male. In some examples,

the CKD is stage 4. In some variations of one or more of the above examples, the subject does not have stage 4 chronic kidney disease (CKD).

In some variations of one or more of the above examples, the subject has diabetic nephropathy (DN) or exhibits one or more symptoms of DN. In some variations of one or more of the above examples, the subject does not have diabetic nephropathy (DN). In some variations of one or more of the above examples, the subject does not exhibit any symptoms of DN. In some examples, the subject has been identified as having DN. In some examples, the subject has been identified as not having DN. In some variations of one or more of the above examples, the level of a marker of DN in the subject has been measured or will be measured.

In some variations of one or more of the above examples, administering the AIM results in an improvement in estimated glomerular filtration rate (eGFR) of the subject. In some examples, the administering reduces the level of serum creatinine in the subject. In some examples, the level of serum creatinine in the blood of the subject has been measured or will be measured. In some variations of one or more of the above examples, the level of blood urea nitrogen (BUN) in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the level of Adiponectin in the blood of the subject has been measured or will be measured.

In some variations of one or more of the above examples, the level of Angiotensin II in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the subject has insulin resistance or exhibits one or more symptoms of insulin resistance. In some variations of one or more of the above examples, the subject does not have insulin resistance. In some variations of one or more of the above examples, the subject does not exhibit any symptoms of insulin resistance. In some examples, the subject has been identified as having insulin resistance. In some examples, the subject has been identified as not having insulin resistance. In some variations of one or more of the above examples, the level of a marker of insulin resistance in the subject has been measured or will be measured. In some examples, the level of hemoglobin A1c in the subject has been measured or will be measured. In some examples, a blood sugar level of the subject has been measured or will be measured. In some examples, the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject. In some examples, a fasting glucose level of the subject has been measured or will be measured. In some examples, the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic

euglycemic clamp test. In some examples, a glucose disposal rate (GDR) in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the subject has glucose intolerance or exhibits one or more symptoms of glucose intolerance. In some variations of one or more of the above examples, the subject does not have glucose intolerance. In some variations of one or more of the above examples, the subject does not exhibit any symptoms of glucose intolerance. In some examples, the subject has been identified as having glucose intolerance. In some examples, the subject has been identified as not having glucose intolerance. In some variations of one or more of the above examples, the level of a marker of glucose intolerance in the subject has been measured or will be measured. In some examples, the level of hemoglobin A1c in the subject has been measured or will be measured. In some examples, a blood sugar level of the subject has been measured or will be measured. In some examples, the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject. In some examples, a fasting glucose level of the subject has been measured or will be measured. In some examples, the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic euglycemic clamp test. In some examples, a glucose disposal rate (GDR) in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the subject has cardiovascular disease (CVD) or exhibits one or more symptoms of CVD. In some variations of one or more of the above examples, the subject does not have cardiovascular disease (CVD) or does not exhibit any symptoms of CVD. In some variations of one or more of the above examples, the subject does not exhibit any symptoms of CVD. In some variations of one or more of the above examples, the subject has been identified as having CVD. In some variations of one or more of the above examples, the subject has been identified as not having CVD. In some variations of one or more of the above examples, the level of a marker of CVD in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the number of circulating endothelial cells (CECs) in the blood of the subject has been measured or will be measured. In some examples, the CECs are iNOS-positive circulating endothelial cells. In some examples, the administering also reduces the level of circulating endothelial cells in the subject. In some examples, the administering also reduces the level of hemoglobin A1c or fasting blood glucose in the subject.

In some variations of one or more of the above examples, the subject has fatty liver disease (FLD) or exhibits one or more symptoms of FLD. In some variations of one or more of the above examples, the subject does not have fatty liver disease (FLD) or does not exhibit any symptoms of FLD. In some variations of one or more of the above examples, the subject does not exhibit any symptoms of FLD. In some variations of one or more of the above examples, the subject has been identified as having FLD. In some variations of one or more of the above examples, the subject has been identified as not having FLD. In some variations of one or more of the above examples, the level of a marker of FLD in the subject has been measured or will be measured.

In some variations of one or more of the above examples, the subject has been identified as having cancer. In some variations of one or more of the above examples, the subject has been identified as not having cancer. In some variations of one or more of the above examples, the subject has been identified as having cancer and diabetes. In some variations of one or more of the above examples, the subject has been identified as not having cancer and/or not having diabetes.

In some variations of one or more of the above examples, if the sufficient amount were administered to a non-obese subject, the non-obese subject's weight would not be reduced significantly.

In some examples, the compound is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir. In some variations, the soft capsule is a gelatin capsule. In variations, the compound is formulated as a solid dispersion. In some variations the hard capsule, soft capsule, tablet or wafer further comprises a protective coating. In some variations, the formulated compound comprises an agent that delays absorption. In some variations, the formulated compound further comprises an agent that enhances solubility or dispersibility. In some variations, the compound is dispersed in a liposome, an oil in water emulsion or a water in oil emulsion.

In some examples, the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound. In some variations, the daily dose is from about 1 mg to about 300 mg of the compound. In some variations, the daily dose is from about 10 mg to about 200 mg of the compound. In some variations, the daily dose is about 25 mg of the compound. In other variations, the daily dose is about 75 mg of the compound. In still other variations, the daily dose is about 150 mg of the compound. In further variations, the daily dose is from about 0.1 mg to about 30 mg of the compound. In some variations, the daily dose is from about 0.5 mg to about 20 mg of the compound. In some

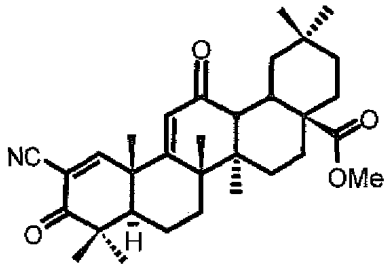
variations, the daily dose is from about 1 mg to about 15 mg of the compound. In some variations, the daily dose is from about 1 mg to about 10 mg of the compound. In some variations, the daily dose is from about 1 mg to about 5 mg of the compound.

In some examples, the pharmaceutically effective amount is a daily dose is 0.01 – 25 mg of compound per kg of body weight. In some variations, the daily dose is 0.05 – 20 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 5 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

In some examples, the pharmaceutically effective amount is administered in a single dose per day. In some examples, the pharmaceutically effective amount is administered in two or more doses per day.

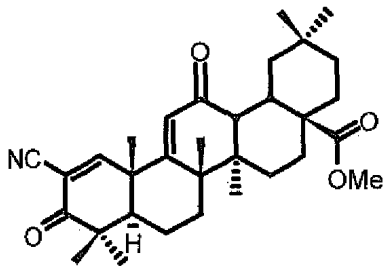
In some examples, the subject is a primate. In some variations, the primate is a human. In other variations, the subject is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

In one aspect, the present invention refers to use of an antioxidant inflammation modulator (AIM) in the manufacture of a medicament for treating an obese or overweight subject by inducing weight loss in the subject in need thereof, wherein said AIM is bardoxolone methyl, where the subject does not have diabetes. In another aspect there is provided a method of reducing a subject's weight comprising administering to the subject a compound of the formula,



in an amount sufficient to reduce the subject's weight, where the subject has been identified as (i) being overweight or obese; and (ii) not having diabetes.

In another aspect, there is provided a method of reducing a subject's weight comprising administering to the subject a compound of the formula,



in an amount sufficient to reduce the subject's weight, wherein:

(a) at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5°2θ, substantially as shown in FIG. 1C, and a T_g from about 120°C to about 135°C; and

(b) where the subject has been identified as

(i) being overweight or obese; and

(ii) not having diabetes.

In some examples, the subject is a human and the amount is a daily dose from 5 mg to 50 mg. In some examples, the daily dose is about 10 mg. In some examples, the daily dose is about 20 mg. In some examples, the daily dose is about 40 mg.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula does not mean that it cannot also belong to another generic formula.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The invention may be better understood by reference to one of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-C – X-ray Powder Diffraction (XRPD) Spectra of Forms A and B of RTA 402. FIG. 1A shows unmicronized Form A; FIG. 1B shows micronized Form A; FIG. 1C shows Form B.

FIG. 2 – Estimated GFR Changes Over Time and Magnitude of Change in Diabetic CKD Patients Treated with Bardoxolone Methyl for 24 Weeks. Estimated GFR changes for patients by dose group at Week 24, based on results of longitudinal model, using the ITT population. Data are depicted as mean ± standard error; n = 57 (placebo, 25 mg, and 75 mg); n = 56 (150 mg).

CLAIMS

Claim 1. Use of an antioxidant inflammation modulator (AIM) in the manufacture of a medicament for treating an obese or overweight subject by inducing weight loss in the subject in need thereof, wherein said AIM is bardoxolone methyl, where the subject does not have diabetes.

Claim 2. The use of claim 1, wherein at least a portion of the bardoxolone methyl is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

Claim 3. The use of claim 2, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

Claim 4. The use of claim 1, wherein at least a portion of the bardoxolone methyl is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g, wherein the T_g value is in the range of 120 °C to 135 °C.

Claim 5. The use of claim 4, wherein the T_g value is in the range of 125 °C to 130 °C.

Claim 6. The use according to any one of claims 1-5, wherein the sufficient amount to reduce the subject's weight is a daily dose from about 0.1 mg to about 30 mg of the AIM.

Claim 7. The use according to any one of claims 1-5, where the AIM is administered orally, intraarterially or intravenously.

Claim 8. The use according to any one of claims 1-5, where the AIM is formulated as a hard or soft capsule or a tablet.

Claim 9. The use according to any one of claims 1-5, wherein the AIM is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

Claim 10. The use of claim 9, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer (1:1).

Claim 11. The use according to any one of claims 1-10, wherein the subject does not also suffer from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer.

Claim 12. The use according to any one of claims 1-10, where the subject has diabetes.

Claim 13. The use according to any one of claims 1-10, where the subject has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.

Claim 14. The use according to any one of claims 1-10, where the subject does not have chronic kidney disease (CKD)

Claim 15. The use according to any one of claims 1-10, where the subject does not have stage 4 chronic kidney disease (CKD).

Claim 16. The use according to any one of claims 1-10, where the subject does not have diabetic nephropathy (DN)

Claim 17. The use according to any one of claims 1-10, where the subject does not exhibit any symptoms of DN.

Claim 18. The use according to any one of claims 1-10, where the subject does not have insulin resistance.

Claim 19. The use according to any one of claims 1-10, where the subject does not have glucose intolerance.

Claim 20. The use according to any one of claims 1-10, where the subject has cardiovascular disease (CVD) or exhibits one or more symptoms of CVD.

Claim 21. The use according to any one of claims 1-10, where the subject does not have cardiovascular disease (CVD) or does not exhibit any symptoms of CVD.

Claim 22. The use according to any one of claims 1-10, where the subject has fatty liver disease (FLD) or exhibits one or more symptoms of FLD.

Claim 23. The use according to any one of claims 1-10, where the subject does not have fatty liver disease (FLD) or does not exhibit any symptoms of FLD.

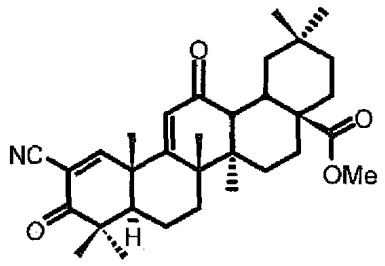
Claim 24. The use according to any one of claims 1-10, where the subject has been identified as having cancer.

Claim 25. The use according to any one of claims 1-10, where the subject has been identified as not having cancer.

Claim 26. The use according to any one of claims 1-10, where the subject has been identified as not having cancer and diabetes.

Claim 27. The use according to any one of claims 1-10, where if the sufficient amount were administered to a non-obese subject, the non-obese subject's weight would not be reduced significantly.

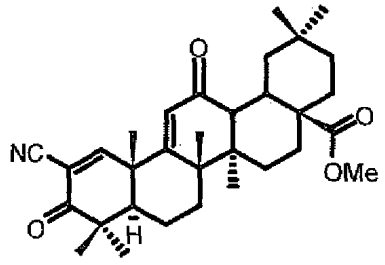
Claim 28. Use of a compound of the formula,



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in the manufacture of a medicament for reducing a subject's weight, where the subject has been identified as (i) being overweight or obese; and (ii) not having diabetes.

Claim 29. Use of a compound of the formula,



,

in the manufacture of a medicament for reducing a subject's weight, wherein:

(a) at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g from about 120 °C to about 135 °C; and

(b) where the subject has been identified as

(i) being overweight or obese; and

(ii) not having diabetes.

Claim 30. The use of claim 29, wherein the subject is a human and the amount is a daily dose from 5 mg to 50 mg.

Claim 31. The use of claim 30, wherein the daily dose is about 10 mg.

Claim 32. The use of claim 30, wherein the daily dose is about 20 mg.

Claim 33. The use of claim 30, wherein the daily dose is about 40 mg.