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(54) Title: CATHEPSIN K INHIBITORS AND OBESITY

(57) Abstract: This invention relates to the treatment of obesity, the treatment of obesity related disorders, prevention of weight gam, prevention of weight regain or for weight maintenance by the use of a cathepsin K inhibitor as active ingredient, alone or in conjunction with other anti-obesity agents The invention also relates to the pharmaceutical compositions comprising cathepsin K inhibitor as active ingredient, pharmaceutically acceptable carriers or excipients, and optionally one or more anti-obesity agents.

TITLE OF THE INVENTION

CATHEPSIN K INHIBITORS AND OBESITY

BACKGROUND OF THE INVENTION

This invention relates to the treatment of obesity, treatment of an obesity related disorder, prevention of weight gain, prevention of weight regain and use for weight maintenance by the administration of a cathepsin K inhibitor, either as a single agent or in combination with other agents.

Cathepsin K expression is upregulated in white adipose tissue in several mouse models of obesity, whereas cathepsin K mRNA levels are not affected in other non-adipose tissues. Cathepsin K expression is induced during differentiation of mouse 3T3-F442A cells into adipocytes. Furthermore, in lean and obese male humans, a significant correlation between cathepsin K gene expression in adipose tissue and body mass index is observed (Chiellini, C. Cell Physiol. 2003, 195:309-21). These data show that a relationship exists between cathepsin K and adipogenesis and obesity.

Cathepsin K may play a key role in adipogenesis and the development of obesity, and cathepsin K inhibitors may be useful for the treatment of obesity and related disorders such as overeating and bulimia, hypertension, type 1 diabetes, type 2 diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer. The compounds of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

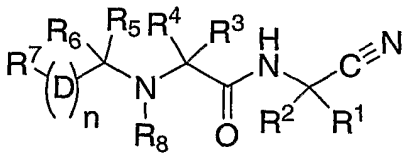
The present data show that genetic ablation of cathepsin K in female mice which were fed a high fat diet for 12 weeks results in a reduction in weight gain and adiposity compared to wild-type littermate female mice.

SUMMARY OF THE INVENTION

The instant invention relates to a method of treating of obesity, treating an obesity related disorder, preventing weight gain, preventing weight regain or using for weight maintenance by the administration of a cathepsin K inhibitor, either as a single agent or in combination with other agents.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to a method of treating of obesity, treating an obesity related disorder, preventing weight gain, preventing weight regain or using for weight maintenance with a cathepsin K inhibitor, either as a single agent or in combination with other agents. In an embodiment of the invention, the cathepsin K inhibitor is a compound of formula I:



I

and the pharmaceutically acceptable salts, esters and solvates thereof wherein:

wherein R^1 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C_{3-6} cycloalkyl, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-OR^9$, $-N(R^{12})_2$, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

R^2 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C_{3-6} cycloalkyl, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-OR^9$, $-N(R^{12})_2$, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring wherein said ring system is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, hydroxyalkyl, haloalkyl, or halo;

R^3 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C_{3-6} cycloalkyl or one to six halo;

R^4 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C_{3-6} cycloalkyl or one to six halo;

or R^3 and R^4 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring, C_{5-8} cycloalkenyl ring, or five to seven membered heterocyclyl wherein said cycloalkyl, cycloalkenyl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

R^5 is selected from hydrogen or C_{1-6} alkyl substituted with 1-6 halo;

R^6 is aryl, heteroaryl, C_{1-6} haloalkyl, arylalkyl or heteroarylalkyl, wherein said aryl, heteroaryl, arylalkyl and heteroarylalkyl groups are optionally substituted with one, two, or three substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, haloalkoxy, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-N(R^{10})(R^{11})$, cyano, or aryl which is optionally substituted with $-SO_2R^{12}$;

each D is independently C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl wherein each said aryl, heteroaryl, cycloalkyl and heterocyclyl groups, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C_{1-6} alkyl, haloalkyl, halo, keto, alkoxy, $-SR^9$, $-SR^{12}$, $-OR^9$, $-OR^{12}$, $N(R^{12})_2$, $-SO_2R^9$, or $-SO_2R^{10}$;

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyloxy, halo, nitro, cyano, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl, $-C(O)OR^{10}$, $-C(O)OSi[CH(CH_3)_2]_3$, $-OR^9$, $-OR^{10}$, $-C(O)R^{10}$, $-R^{10}C(O)R^9$, $-C(O)R^9$, $-C(O)N(R^a)(R^b)$, $-C(O)N(R^{12})(R^{12})$, $-C(O)N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})OH$, $-SR^{12}$, $-SR^9$, $-R^{10}SR^9$, $-R^9$, $-C(R^9)_3$, $-C(R^{10})(R^{11})N(R^9)_2$, $-NR^{10}C(O)NR^{10}S(O)_2R^9$, $-SO_2R^{12}$, $-SO(R^{12})$, $-SO_2R^9$, $-SO_mN(R^c)(R^d)$, $-SO_mCH(R^{10})(R^{11})$, $-SO_2N(R^{10})C(O)(R^{12})$, $-SO_2(R^{10})C(O)N(R^{12})_2$, $-OSO_2R^{10}$, $-N(R^{10})(R^{11})$, $-N(R^{10})C(O)N(R^{10})(R^9)$, $-N(R^{10})C(O)R^9$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)OR^{10}$, $-N(R^{10})SO_2(R^{10})$, $-C(R^{10})(R^{11})NR^{10}C(R^{10})(R^{11})R^9$, $-C(R^{10})(R^{11})N(R^{10})R^9$, $-C(R^{10})(R^{11})N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})SC(R^{10})(R^{11})(R^9)$, $R^{10}S-$, $-C(R^a)(R^b)NR^aC(R^a)(R^b)(R^9)$, $-C(R^a)(R^b)N(R^a)(R^b)$, $-C(R^a)(R^b)C(R^a)(R^b)N(R^a)(R^b)$, $-C(O)C(R^a)(R^b)N(R^a)(R^b)$, $-C(R^a)(R^b)N(R^a)C(O)R^9$, $-C(O)C(R^a)(R^b)S(R^a)$, $C(R^a)(R^b)C(O)N(R^a)(R^b)$, $-B(OH)_2$, $-OCH_2O-$ or 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl; wherein said groups are optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C_{1-6} alkyl, halo, keto, cyano, haloalkyl, hydroxyalkyl, $-OR^9$, $-NO_2$, $-NH_2$, $-NHS(O)_2R^8$, $-R^9SO_2R^{12}$, $-SO_2R^{12}$, $-SO(R^{12})$, $-SR^{12}$, $-SR^9$, $-SO_mN(R^c)(R^d)$, $-SO_mN(R^{10})C(O)(R^{12})$, $-C(R^{10})(R^{11})N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})OH$, $-COOH$, $-C(R^a)(R^b)C(O)N(R^a)(R^b)$, $-C(O)(R^a)(R^b)$, $-N(R^{10})C(R^{10})(R^{11})(R^9)$, $-N(R^{10})CO(R^9)$, $-NH(CH_2)_2OH$, $-NHC(O)OR^{10}$, $-Si(CH_3)_3$, heterocycyl, aryl, or heteroaryl ;

R^8 is hydrogen or C_{1-6} alkyl;

or R^4 and R^8 or can be taken together with any of the atoms to which they may be attached or are between them to form a 4-10 membered heterocyclyl ring system wherein said ring system, which may be monocyclic or bicyclic, is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, keto, $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$;

R^9 is selected from the group consisting of hydrogen, aryl, aryl(C_{1-4}) alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl(C_{1-4})alkyl, and heterocyclyl(C_{1-4})alkyl wherein said groups can be optionally substituted with one, two, or three substituents independently selected from halo, alkoxy or $-SO_2R^{12}$;

R^{10} is hydrogen or C_{1-6} alkyl

R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, $-NR^{10}$ or $-SR^{10}$;
R^a is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)aryl, (C_{1-6} alkyl)hydroxyl, $-O(C_{1-6}$ alkyl), hydroxyl, halo, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl, wherein said alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl can be optionally substituted on either the carbon or the heteroatom with one, two, or three substituents independently selected from C_{1-6} alkyl or halo;
R^b is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)aryl, (C_{1-6} alkyl)hydroxyl, alkoxyl, hydroxyl, halo, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl,wherein said alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl can be optionally substituted on either the carbon or the heteroatom with one, two, or three substituents independently selected from C_{1-6} alkyl or halo;
or R^a and R^b can be taken together with the carbon atom to which they are attached or are between them to form a C_{3-8} cycloalkyl ring or C_{3-8} heterocyclyl ring wherein said 3-8 membered ring system may be optionally substituted with one or two substituents independently selected from C_{1-6} alkyl and halo;
R^c is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or $-OR^9$;
R^d is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or $-OR^9$;
or R^c and R^d can be taken together with the nitrogen atom to which they are attached or are between them to form a C_{3-8} heterocyclyl ring which is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, halo hydroxyalkyl, hydroxy, alkoxy or keto;
n is independently selected from an integer from zero to three;
each m is independently selected from an integer from zero to two;
and the pharmaceutically acceptable salts, stereoisomers and N-oxide derivatives thereof.

Nonlimiting examples of compound of formula I include:

N^1-(1-cyanocyclopropyl)-4-fluoro- N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^1-(1-cyanocyclopropyl)-4-fluoro-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfinyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^1(cyanomethyl)-N^2-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^2-{(1S)-1-[4'-(aminosulfonyl)-1,1'-biphenyl-4-yl]-2,2,2-trifluoroethyl}-N^1(cyanomethyl)-L-leucinamide;
N^1(1-cyanocyclopropyl)- N^2-{(1S)-2,2-difluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-4-fluoro-L-leucinamide;
and the pharmaceutically acceptable salts thereof.

Methods of preparation for the above compounds are described in International Publication WO 03/075836, which published on September 18, 2003.

Nonlimiting examples of cathepsin K inhibitors of the present invention also include:
N-(1-{[(cyanomethyl)amino]carbonyl}cyclohexyl)-4-(4-propylpiperazin-1-yl)benzamide;
N-(1-{[(cyanomethyl)amino]carbonyl}cyclohexyl)-4-[1-(2-methoxyethyl)piperidin-4-yl]benzamide;

and the pharmaceutically acceptable salts thereof. Methods of preparation for these compounds are described in International Publication WO 99/24460, which published on May 20, 1999.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms unless otherwise specified. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above, unless otherwise indicated, wherein said alkyl group is attached through an oxygen bridge.

The term "cycloalkyl" or "carbocycle" shall mean cyclic rings of alkanes of three to eight total carbon atoms, unless otherwise indicated, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least 1 carbon to carbon double bond. Preferably 1 carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "cycloalkenyl" shall mean cyclic rings of 3 to 10 carbon atoms, unless otherwise specified, containing at least 1 carbon to carbon double bond (i.e., cyclopropenyl, cyclobutenyl, cyclopenentyl, cyclohexenyl, cycloheptenyl or cycloocentyl).

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, containing at least 1 carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, CH(CH_3) CH_2CH(CH_3)Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, and tetrahydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "keto" means carbonyl (C=O). The term "alkoxy" as used herein means an alkyl portion, where alkyl is as defined above, connected to the remainder of the molecule via an oxygen atom. Examples of alkoxy include methoxy, ethoxy and the like.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, and the like.

The term "haloalkoxy" represents a radical –OR where R is alkyl as defined above that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyloxy, dichloroethyloxy, and the like.

The term "arylalkyl" includes an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, and chlorophenylethyl. Examples of alkylaryl include, but are not limited to, toluyl, ethylphenyl, and propylphenyl.

The term "heteroarylalkyl" as used herein, shall refer to a system that includes a heteroaryl portion, where heteroaryl is as defined above, and contains an alkyl portion. Examples of heteroarylalkyl include, but are not limited to, thienylmethyl, thienylethyl, thienylpropyl, pyridylmethyl, pyridylethyl and imidazoylmethyl.

The term "cycloalkylalkyl" includes an alkyl portion where alkyl is as defined above and also includes an cycloalkyl portion where cycloalkyl is as defined above. Examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, and the like.

The term "hydroxyalkyl" means a linear monovalent hydrocarbon raidcal of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3- hydroxypropyl, and the like.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO_2 and includes bicyclic groups. "Heterocyclyl" therefore includes, but is not limited to the following: piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also emcompassed by this definition.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can beconverted to an N-oxide by methods well known in the art. Also whencompounds of Formula I contain groups such as hydroxy, carboxy, thiol or anygroup containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C_{0-8} alkyl) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The cathepsin K inhibitor compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, topical (e.g., ocular

eyedrop), subcutaneous, intramuscular or transdermal (e.g., patch) form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the cathepsin K inhibitor compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the cathepsin K inhibitor compounds, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, cathepsin K inhibitor compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred cathepsin K inhibitor compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

Exemplifying the invention is a pharmaceutical composition comprising a cathepsin K inhibitor, an anti-obesity agent and a pharmaceutically acceptable carrier. Further illustrating the invention is the use of an cathepsin K inhibitor, an anti-obesity agent and a pharmaceutically acceptable carrier for the preparation of a medicament useful in the treatment of obesity. In an embodiment of the invention, the anti-obesity agent is: PYY, PYY_{3-36}, a PYY agonist, 5HT transporter inhibitor; NE transporter inhibitor; ghrelin antagonist; H3 antagonist/inverse agonist; MCH1R antagonist; MCH2R agonist/antagonist; MC3R agonist; NPY1 antagonist; NPY4 agonist; NPY5 antagonist; leptin; leptin agonist/modulator; leptin derivatives; opioid antagonist; orexin antagonist; BRS3 agonist; 11β HSD-1 inhibitor; CCK-A agonist; CNTF; CNTF agonist/modulator; CNTF derivative; Cox-2 inhibitor; GHS agonist; 5HT2C agonist; 5HT6 antagonist; monoamine reuptake inhibitor; UCP-1, 2, and 3 activator; β3

agonist; thyroid hormone β agonist; PDE inhibitor; FAS inhibitor; DGAT1 inhibitor; DGAT2 inhibitor; ACC2 inhibitor; glucocorticoid antagonist; acyl-estrogens; lipase inhibitor; fatty acid transporter inhibitor; dicarboxylate transporter inhibitor; glucose transporter inhibitor; serotonin reuptake inhibitors; aminorex; amphechloral; amphetamine; axokine; benzphetamine; chlorphentermine; clobenzorex; cloforex; clominorex; clortermine; cyclexedrine; dextroamphetamine; diphemethoxidine,N-ethylamphetamine;fenbutrazate; fenisorex;fenproporex; fludorex; fluminorex; furfurylmethylamphetamine; levamfetamine; levophacetoperane; mefenorex; metamfepramone; methamphetamine; nalmefene; norpseudoephedrine; pentorex; phendimetrazine; phenmetrazine; phytopharm compound 57; picilorex; topiramate; zonisamide; or a combination thereof.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The cathepsin K inhibitor compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Cathepsin K inhibitor compounds may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a cathepsin K inhibitor and one or more other

pharmacologically active agents suitable for the treatment of obesity. The cathepsin K inhibitor and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination. For example, the present compound may be employed directly in combination with the other active agent(s), or it may be administered prior, concurrent or subsequent to the administration of the other active agent(s). In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

The cathepsin K inhibitors of the present invention can be used for the treatment of obesity or obesity related disorders comprising administering a therapeutically effective amount of a cathepsin K inhibitor to a patient in need of such treatment. A further aspect of this invention involves a method for preventing or reducing the risk of developing obesity, comprising administering a prophylactically effective amount of a cathepsin K inhibitor to a patient in need of such treatment. In an embodiment of the invention, obesity related disorders include, but are not limited to: diabetes, non-insulin dependent diabetes mellitus - type II (2), impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, metabolic syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, infertility, overeating; bulimia, elevated plasma insulin concentrations, hyperlipidemia, endometrial, cancer, breast cancer, prostate cancer, colon cancer, osteoarthritis, cholelithiasis, gallstones, coronary heart disease, abnormal heart rhythms, heart arrythmias, myocardial infarction, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, or acute lymphoblastic leukemia.

"Obesity" is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). "Obesity" refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m^2, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m^2. An "obese subject" is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2. A "subject at risk of obesity" is an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2 or a subject with at least one co-morbidity with a BMI of 25 kg/m^2 to less than 27 kg/m^2.

The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, "obesity" refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity, that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m^2. In Asian countries, including Japan, an "obese subject" refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with

a BMI greater than or equal to 25 kg/m^2. In Asia-Pacific, a "subject at risk of obesity" is a subject with a BMI of greater than 23 kg/m^2 to less than 25 kg/m^2.

As used herein, the term "obesity" is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes, non-insulin dependent diabetes mellitus - type II (2), impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, metabolic syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, diabetes mellitus, and other obesity-related conditions.

Prevention of weight regain, prevention of weight gain and use for weight maintenance refer to the administration of the compounds or combinations of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders.

"Treatment" (of obesity and obesity-related disorders) refers to the administration of the compounds or combinations of the present invention to reduce food intake, to reduce body weight, or to maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. Another outcome of treatment may be to maintain weight loss. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

"Prevention" (of obesity and obesity-related disorders) refers to the administration of the compounds or combinations of the present invention to reduce food intake, to reduce body weight, or to maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be to prolong resistance to weight gain. Another outcome of prevention may be to prevent weight regain. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, metabolic syndrome, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

The obesity-related disorders herein are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, reproductive hormone abnormalities, sexual and reproductive dysfunction, such as impaired fertility, infertility, hypogonadism in males and hirsutism in females, fetal defects associated with maternal obesity, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), breathlessness, cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, kidney cancer, and increased anesthetic risk. The combinations of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy. The combinations of the present invention are also useful to treat Alzheimer's disease.

The cathepsin K inhibitors are also useful for treating or preventing obesity and obesity-related disorders in cats and dogs. As such, the term "mammal" includes companion animals such as cats and dogs.

The term "metabolic syndrome", also known as syndrome X, is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP-III). E.S. Ford et al., JAMA, vol. 287 (3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the following symptoms: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-III.

The term "diabetes," as used herein, includes both insulin-dependent diabetes mellitus (i.e., IDDM, also known as type I diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also known as Type II diabetes). Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese. The compositions of the present invention are useful for treating both Type I and Type II diabetes. The compositions are especially effective for treating Type II diabetes. The compounds or combinations of the present invention are also useful for treating and/or preventing gestational diabetes mellitus.

A therapeutically effective amount of a cathepsin K inhibitor can be used for the preparation of a medicament useful for treating or preventing any of the medical conditions described herein, in dosage amounts described herein. Additionally, the medicament may be useful for preventing or reducing the risk of developing obesity, halting or slowing the progression of obesity once it has become clinically manifest. The medicament comprised of a compound of Formula I may also be prepared with one or more additional active agents, such as those described herein.

In a broad embodiment, any suitable additional active agent or agents, including but not limited to anti-obesity agents, may be used in combination with the compound of formula I in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a compound of Formula I. The additional active agent or agents can be lipid modifying compounds or agents having other pharmaceutical activities, or agents that have both lipid-modifying effects and other pharmaceutical activities.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of another agent useful in treating obesity and obesity-related conditions, such that together they give effective relief.

Cathepsin K inhibitors may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which cathepsin K

inhibitors are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a cathepsin K inhibitor. When a cathepsin K inhibitor is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the cathepsin K inhibitor is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a cathepsin K inhibitor.

Examples of other active ingredients that may be combined with a cathepsin K inhibitor for the treatment or prevention of obesity and/or diabetes, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) insulin sensitizers including (i) PPARγ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTZD), GW-0207, LG-100641, and LY-300512, and the like), and compounds disclosed in WO 97/10813, WO 97/27857, WO 97/28115, WO 97/28137, and WO 97/27847; (iii) biguanides such as metformin and phenformin;

(b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH_2);

(c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide;

(d) α-glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like;

(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®, and the like, (ii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics;

(f) PPARα agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and the like, and PPARα agonists as described in WO 97/36579 by Glaxo;

(g) PPARδ agonists, such as those disclosed in WO97/28149;

(h) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002; and

(i) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255, and such as those disclosed in U.S. Patent Nos. 5,536,716, and 6,358,951, U.S. Patent Application Nos. 2002/049196 and 2002/022637, and PCT Application Nos. WO 01/56592 and WO 02/32888; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB_1 receptor antagonists or inverse agonists, such as rimonabant (Sanofi Synthelabo), AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer), and those disclosed in U.S. Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, PCT Application Nos. WO 96/33159, WO 98/33765, WO98/43636, WO98/43635, WO 01/09120, WO98/31227, WO98/41519, WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, W002/076949, and WO 03/007887; and EPO Application No. EP-658546, EP-656354, EP-576357; (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A, and such as those disclosed in U.S. Patent Application Nos. 5,705,515, and US 5,451,677 and PCT Patent Publications WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO 01/74782, and WO 02/32897; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate, and those disclosed in PCT Application No. WO 01/77094; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in U.S. Patent No. 6,001,836, and PCT Patent Publication Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104, and those disclosed in U.S. Patent Nos. 6,057,335; 6,043,246; 6,140,354; 6,166,038; 6,180,653; 6,191,160; 6,313,298; 6,335,345; 6,337,332; 6,326,375; 6,329,395; 6,340,683; 6,388,077; 6,462,053; 6,649,624; and 6,723,847, hereby incorporated by reference in their entirety; European Patent Nos. EP-01010691, and EP-01044970; and PCT International Patent Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/24768; WO 98/25907; WO 98/25908; WO 98/27063, WO 98/47505; WO 98/40356; WO 99/15516; WO 99/27965; WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376; WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, and WO 02/49648; WO 02/094825; WO 03/014083; WO 03/10191; WO 03/092889; WO 04/002986; and WO 04/031175 (9) melanin-concentrating hormone (MCH) receptor antagonists, such as those disclosed in WO 01/21577 and WO 01/21169; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), and those disclosed in PCT Patent Application Nos. WO 01/82925, WO

01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027, and Japanese Patent Application Nos. JP 13226269, and JP 2004-139909; (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin-1 receptor antagonists, such as SB-334867-A, and those disclosed in PCT Patent Application Nos. WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline, and those disclosed in U.S. Patent Application No. 6,365,633, and PCT Patent Application Nos. WO 01/27060 and WO 01/162341; (14) melanocortin agonists, such as Melanotan II or those described in WO 99/64002 and WO 00/74679; (15) other Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin), and those disclosed in: US Patent Nos. 6,410,548; 6,294,534; 6,350,760; 6,458,790; 6,472,398; and 6,376,509; US Patent Publication No. US2004/009751, and PCT Application Nos. WO 99/64002; WO 00/74679; WO 01/70708; WO 01/70337; WO 01/74844; WO 01/91752; WO 01/991752; WO 02/059095; WO 02/059107; WO 02/059108; WO 02/059117; WO 02/068387; WO 02/068388; WO 02/067869; WO 02/11715; WO 02/12166; WO 02/12178; WO 03/007949; and WO 03/009847; (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065, and those disclosed in U.S. Patent No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; (18) galanin antagonists; (19) CCK agonists; (20) CCK-A (cholecystokinin –A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR146131, and those discribed in U.S. Patent No. 5,739,106; (21) GLP-1 agonists; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and those described and disclosed in PCT Application No. WO 02/15905, and O-[3-(1H-imidazol-4-yl)propanol]-carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)); (25) β-hydroxy steroid dehydrogenase-1 inhibitors (β-HSD-1); 26) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists, such as those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives, such as those disclosed in U.S. Patent Nos. 5,552,524, 5,552,523, 5,552,522, 5,521,283, and PCT International Publication Nos. WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519, and WO 96/23520; (32) BRS3 (bombesin

receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron), and those disclosed in PCT Application Nos. WO 94/09134, WO 98/22128, and WO 99/43813; (35) monoamine reuptake inhibitors, such as sibutramine, and those disclosed in U.S. Patent Nos. 4,746,680, 4,806,570, and 5,436,272, U.S. Patent Publication No. 2002/0006964 and PCT Application Nos. WO 01/27068, and WO 01/62341; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in PCT Patent Application No. WO 99/00123; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in PCT Application No. WO 02/15845, and Japanese Patent Application No. JP 2000256190; (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444; and the compounds disclosed in US Patent No. US 6,699,871, specifically the dihydrogenphosphate salt of 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, which is incorporated herein by reference; and International Patent Application Nos. WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180; and WO 03/000181; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); and (50) Topiramate (Topimax®); and (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)), and those disclosed in US 5,026,685, US 5,604,203, US 5,574, 010, US 5, 696,093, US 5,936,092, US 6,046, 162, US 6,046,167, US, 6,093,692, US 6,225,445, U.S. 5,604,203, US 4,002,531, US 4, 179,337, US 5,122,614, US 5,349,052, US 5,552,520, US 6, 127,355, WO 95/06058, WO 98/32466, WO 03/026591, WO 03/057235, WO 03/027637, and WO 2004/066966, which are incorporated herein by reference; (51) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP) as described in Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91; (54) cyclo-oxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381, and pharmaceutically acceptable salts thereof; (55) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A and those disclosed in U.S. Patent No. 6,001,836; and PCT Application Nos. WO

96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone, and those disclosed in: PCT Application No. WO 00/21509; (57) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitor such as BVT 3498, BVT 2733, and those disclosed in WO 01/90091, WO 01/90090, WO 01/90092, and US Patent No. US 6,730,690 and US Publication No. US 2004-0133011, which are incorporated by reference herein in their entirety; and (58) aminorex; (59) amphechloral; (60) amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72) fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80) metamfepramone; (81) methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; and (88) zonisamide.

Specific NPY5 antagonists of use in combination with a compound of the present invention are selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide,

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide,

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide,

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide,

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide,

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran- 1(3H),1'-cyclohexane]-4'-carboxamide,

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, and pharmaceutically acceptable salts and esters thereof.

Examples of other anti-obesity agents that can be employed in combination with a compound of Formula I and Formula VI are disclosed in "Patent focus on new anti-obesity agents," Exp. Opin. Ther. Patents, 10: 819-831 (2000); "Novel anti-obesity drugs," Exp. Opin. Invest. Drugs, 9: 1317-1326 (2000); and "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity, Exp. Opin. Ther. Patents, 11: 1677-1692 (2001). The role of neuropeptide Y in obesity is discussed in Exp. Opin. Invest. Drugs, 9: 1327-1346 (2000). Cannabinoid receptor ligands are discussed in Exp. Opin. Invest. Drugs, 9: 1553-1571 (2000). Various pharmacological approaches for the treatment of obesity are discussed in J-A Fernandez-Lopez, Drugs: 62: 915-944 (2002) and in H. Bays, et al., "Anti-obesity drug development," Exp. Opin. Invest. Drugs, 11: 1189-1204 (2002).

The above compounds are only illustrative of the anti-obesity agents that can be used in combination with the compounds of the present invention. As this listing of compounds is not meant to be comprehensive, the methods of the present invention may employ any anti-obesity agent, and are not limited to any particular structural class of compounds.

The combinations of the present invention are useful for the treatment or prevention of disorders associated with excessive food intake, such as obesity and obesity-related disorders. The obesity herein may be due to any cause, whether genetic or environmental.

ASSAYS

Cathepsin K Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human cathepsin K (0.4 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Effect of Cathepsin K gene deletion on mouse body weight increase, percentage body fat and plasma lipids after 12 weeks on a high fat diet

Cathepsin K homozygous null (KO, Saftig P et al, Proc Natl Acad Sci U S A. 1998; 95 :13453-8) and wild-type littermate controls (WT, mixed 129/C57BL/6 background) were fed a high fat diet (HFD, 35% fat, 35% carbohydrate by weight, Bio-Serv (F3282), n=10-12/group) for 12 weeks starting at an age of

age approximately 8 weeks. The animals were weighed weekly and food consumption was determined. No difference in food consumption between groups was detected. The percentage of body fat for each animal was determined using dual energy X-ray absorptiometry after 12 weeks on the HFD. At termination, blood was taken for determination of plasma cholesterol triglycerides and leptin.

	Male WT	Male KO	Female WT	Female KO
Body weight gain after 12 weeks on HFD	14.9 ± 2.0[a]	12.9 ± 1.8	13.4 ± 2.3	6.8 ± 1.6**
% body fat after 12 weeks on HFD	32.8 ± 2.7	32.5 ± 1.0	33.7 ± 3.8	22.1 ± 2.8*
Plasma cholesterol (mM)	5.19 ± 0.24	3.65 ± 0.27**	3.73 ± 0.27	3.14 ± 0.12*
Plasma triglycerides (mM)	1.76 ± 0.11	1.42 ± 0.07*	1.64 ± 0.17	1.59 ± 0.08
Plasma leptin (ng/mL)	83.75 ± 14.46	37.25 ± 5.30*	32.24 ± 8.73	13.68 ± 5.91*

[a] ± SEM. *p<0.05, **p<0.01, vs WT

Differentiation of 3T3-L1 fibroblasts to adipocytes in the presence of Cathepsin K inhibitors

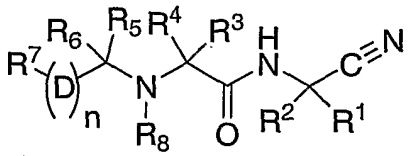
3T3-L1 fibroblasts were seeded in 6-well plates, grown to confluence in regular DMEM media (containing high glucose, 10 % serum, 1% antibiotic P/S, 10 mM HEPES) and maintained at confluence for 2 days. Cells were differentiated to an adipocyte phenotype using a 6-day protocol as follows. Cells were cultured in DMEM media containing insulin (5 μg/mL), IBMX (0.5 μM) and dexamethasone (0.25 μM) for 2 days, after which IBMX and dexamethasone were removed. Cells were incubated for a further 2 days in DMEM media containing insulin and then subsequently for 2 further days in DMEM media. Fat droplets (adipocytes) were usually observed after 4 days.

Cathepsin K inhibitors were tested at concentrations of 1 nM to 1 mM and were present in the various media from day 0. At day +4, fat droplets were observed in control cells, whereas cells with the cathepsin inhibitors had conserved their fibroblast phenotype.

WHAT IS CLAIMED:

1. A method for treating obesity, treating an obesity related disorder, preventing weight gain, preventing weight regain or using for weight maintenance comprising administering a therapeutically effective amount of a cathepsin K inhibitor.

2. The method of Claim 1 wherein the cathepsin K inhibitor is represented by formula I:



I

wherein R^1 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C_{3-6} cycloalkyl, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-OR^9$, $-N(R^{12})_2$, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

R^2 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C_{3-6} cycloalkyl, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-OR^9$, $-N(R^{12})_2$, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl or heterocyclyl ring wherein said ring system is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, hydroxyalkyl, haloalkyl, or halo;

R^3 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C_{3-6} cycloalkyl or one to six halo;

R^4 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C_{3-6} cycloalkyl or one to six halo;

or R^3 and R^4 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring, C_{5-8} cycloalkenyl ring, or five to seven membered heterocyclyl wherein said cycloalkyl, cycloalkenyl and heterocyclyl groups are optionally substituted with one or two substitutents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, alkoxy or keto;

R^5 is selected from hydrogen or C_{1-6} alkyl substituted with 1-6 halo;

R^6 is aryl, heteroaryl, C_{1-6} haloalkyl, arylalkyl or heteroarylalkyl, wherein said aryl, heteroaryl, arylalkyl and heteroarylalkyl groups are optionally substituted with one, two, or three substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, haloalkoxy, $-SR^9$, $-SR^{12}$, $-SOR^9$, $-SOR^{12}$, $-SO_2R^9$, $-SO_2R^{12}$, $-SO_2CH(R^{12})(R^{11})$, $-OR^{12}$, $-N(R^{10})(R^{11})$, cyano, or aryl which is optionally substituted with $-SO_2R^{12}$;

each D is independently C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl wherein each said aryl, heteroaryl, cycloalkyl and heterocyclyl groups, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C_{1-6} alkyl, haloalkyl, halo, keto, alkoxy, $-SR^9$, $-SR^{12}$, $-OR^9$, $-OR^{12}$, $N(R^{12})_2$, $-SO_2R^9$, or $-SO_2R^{10}$;

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyloxy, halo, nitro, cyano, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl, $-C(O)OR^{10}$, $-C(O)OSi[CH(CH_3)_2]_3$, $-OR^9$, $-OR^{10}$, $-C(O)R^{10}$, $-R^{10}C(O)R^9$, $-C(O)R^9$, $-C(O)N(R^a)(R^b)$, $-C(O)N(R^{12})(R^{12})$, $-C(O)N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})OH$, $-SR^{12}$, $-SR^9$, $-R^{10}SR^9$, $-R^9$, $-C(R^9)_3$, $-C(R^{10})(R^{11})N(R^9)_2$, $-NR^{10}C(O)NR^{10}S(O)_2R^9$, $-SO_2R^{12}$, $-SO(R^{12})$, $-SO_2R^9$, $-SO_mN(R^c)(R^d)$, $-SO_mCH(R^{10})(R^{11})$, $-SO_2N(R^{10})C(O)(R^{12})$, $-SO_2(R^{10})C(O)N(R^{12})_2$, $-OSO_2R^{10}$, $-N(R^{10})(R^{11})$, $-N(R^{10})C(O)N(R^{10})(R^9)$, $-N(R^{10})C(O)R^9$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)OR^{10}$, $-N(R^{10})SO_2(R^{10})$, $-C(R^{10})(R^{11})NR^{10}C(R^{10})(R^{11})R^9$, $-C(R^{10})(R^{11})N(R^{10})R^9$, $-C(R^{10})(R^{11})N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})SC(R^{10})(R^{11})(R^9)$, $R^{10}S-$, $-C(R^a)(R^b)NR^aC(R^a)(R^b)(R^9)$, $-C(R^a)(R^b)N(R^a)(R^b)$, $-C(R^a)(R^b)C(R^a)(R^b)N(R^a)(R^b)$, $-C(O)C(R^a)(R^b)N(R^a)(R^b)$, $-C(R^a)(R^b)N(R^a)C(O)\,R^9$, $-C(O)C(R^a)(R^b)S(R^a)$, $C(R^a)(R^b)C(O)N(R^a)(R^b)$, $-B(OH)_2$, $-OCH_2O-$ or 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl; wherein said groups are optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C_{1-6} alkyl, halo, keto, cyano, haloalkyl, hydroxyalkyl, $-OR^9$, $-NO_2$, $-NH_2$, $-NHS(O)_2R^8$, $-R^9SO_2R^{12}$, $-SO_2R^{12}$, $-SO(R^{12})$, $-SR^{12}$, $-SR^9$, $-SO_mN(R^c)(R^d)$, $-SO_mN(R^{10})C(O)(R^{12})$, $-C(R^{10})(R^{11})N(R^{10})(R^{11})$, $-C(R^{10})(R^{11})OH$, $-COOH$, $-C(R^a)(R^b)C(O)N(R^a)(R^b)$, $-C(O)(R^a)(R^b)$, $-N(R^{10})C(R^{10})(R^{11})(R^9)$, $-N(R^{10})CO(R^9)$, $-NH(CH_2)_2OH$, $-NHC(O)OR^{10}$, $-Si(CH_3)_3$, heterocycyl, aryl, or heteroaryl ;

R^8 is hydrogen or C_{1-6} alkyl;

or R^4 and R^8 or can be taken together with any of the atoms to which they may be attached or are between them to form a 4-10 membered heterocyclyl ring system wherein said ring system, which may be monocyclic or bicyclic, is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, halo, hydroxyalkyl, hydroxy, keto, $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$;

R^9 is selected from the group consisting of hydrogen, aryl, aryl(C_{1-4}) alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl(C_{1-4})alkyl, and heterocyclyl(C_{1-4})alkyl wherein said groups can be optionally substituted with one, two, or three substituents independently selected from halo, alkoxy or $-SO_2R^{12}$;

R^{10} is hydrogen or C_{1-6} alkyl

R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, $-NR^{10}$ or $-SR^{10}$;

R^a is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)aryl, (C_{1-6} alkyl)hydroxyl, $-O(C_{1-6}$ alkyl), hydroxyl, halo, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl, wherein said alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl can be optionally substituted on either the carbon or the heteroatom with one, two, or three substituents independently selected from C_{1-6} alkyl or halo;

R^b is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)aryl, (C_{1-6} alkyl)hydroxyl, alkoxyl, hydroxyl, halo, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl,wherein said alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl can be optionally substituted on either the carbon or the heteroatom with one, two, or three substituents independently selected from C_{1-6} alkyl or halo;
or R^a and R^b can be taken together with the carbon atom to which they are attached or are between them to form a C_{3-8} cycloalkyl ring or C_{3-8} heterocyclyl ring wherein said 3-8 membered ring system may be optionally substituted with one or two substituents independently selected from C_{1-6} alkyl and halo;

R^c is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or $-OR^9$;

R^d is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or $-OR^9$;
or R^c and R^d can be taken together with the nitrogen atom to which they are attached or are between them to form a C_{3-8} heterocyclyl ring which is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, halo hydroxyalkyl, hydroxy, alkoxy or keto;

n is independently selected from an integer from zero to three;
each m is independently selected from an integer from zero to two;
and the pharmaceutically acceptable salts, stereoisomers and N-oxide derivatives thereof.

3. The method of Claim 2 wherein the cathepsin K inhibitor is
N^1-(1-cyanocyclopropyl)-4-fluoro- N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^1-(1-cyanocyclopropyl)-4-fluoro-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfinyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^1(cyanomethyl)-N^2{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide;
N^2{(1S)-1-[4'-(aminosulfonyl)-1,1'-biphenyl-4-yl]-2,2,2-trifluoroethyl}-N^1(cyanomethyl)-L-leucinamide;
N^1(1-cyanocyclopropyl)- N^2-{(1S)-2,2-difluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-4-fluoro-L-leucinamide;
or a pharmaceutically acceptable salt thereof.

4. The method of Claim 1 wherein the cathepsin K inhibitor is
N-(1-{[(cyanomethyl)amino]carbonyl}cyclohexyl)-4-(4-propylpiperazin-1-yl)benzamide;
N-(1-{[(cyanomethyl)amino]carbonyl}cyclohexyl)-4-[1-(2-methoxyethyl)piperidin-4-yl]benzamide;
or a pharmaceutically acceptable salt thereof.

5. The method of Claim 1 wherein the obesity related disorder is diabetes, non-insulin dependent diabetes mellitus - type II (2), impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, metabolic syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, infertility, overeating, bulimia, elevated plasma insulin concentrations, hyperlipidemia, endometrial cancer, breast cancer, prostate cancer, colon cancer, osteoarthritis, cholelithiasis, gallstones, coronary heart disease, abnormal heart rhythms, heart arrythmias, myocardial infarction, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, or acute lymphoblastic leukemia.

6. The method of Claim 5 further comprising an anti-obesity agent.

7. The method of Claim 6 wherein the anti-obesity agent is an anti-diabetic agent, a lipid lowering agent or an anti-hypertensive agent.

8. The method of Claim 6 wherein the anti-obesity agent is PYY; PYY_{3-36}; a PYY agonist; 5HT transporter inhibitor; NE transporter inhibitor; ghrelin antagonist; H3 antagonist/inverse agonist; MCH1R antagonist; MCH2R agonist/antagonist; MC3R agonist; NPY1 antagonist; NPY4 agonist; NPY5 antagonist; leptin; leptin agonist/modulator; leptin derivatives; opioid antagonist; orexin antagonist; BRS3 agonist; 11β HSD-1 inhibitor; CCK-A agonist; CNTF; CNTF agonist/modulator;

CNTF derivative; Cox-2 inhibitor; GHS agonist; 5HT2C agonist; 5HT6 antagonist; monoamine reuptake inhibitor; UCP-1, 2, and 3 activator; β3 agonist; thyroid hormone β agonist; PDE inhibitor; FAS inhibitor; DGAT1 inhibitor; DGAT2 inhibitor; ACC2 inhibitor; glucocorticoid antagonist; acyl-estrogens; lipase inhibitor; fatty acid transporter inhibitor; dicarboxylate transporter inhibitor; glucose transporter inhibitor; serotonin reuptake inhibitors; aminorex; amphechloral; amphetamine; axokine; benzphetamine; chlorphentermine; clobenzorex; cloforex; clominorex; clortermine; cyclexedrine; dextroamphetamine; diphemethoxidine, N-ethylamphetamine;fenbutrazate; fenisorex;fenproporex; fludorex; fluminorex; furfurylmethylamphetamine; levamfetamine; levophacetoperane; mefenorex; metamfepramone; methamphetamine; nalmefene; norpseudoephedrine; pentorex; phendimetrazine; phenmetrazine;
phytopharm compound 57; picilorex; topiramate; zonisamide; or a combination thereof.

9. A pharmaceutical composition comprising a cathepsin K inhibitor and an anti-obesity agent.

10. The pharmaceutical composition of Claim 9 wherein the anti-obesity agent is PYY; PYY_{3-36}; a PYY agonist; 5HT transporter inhibitor; NE transporter inhibitor; ghrelin antagonist; H3 antagonist/inverse agonist; MCH1R antagonist; MCH2R agonist/antagonist; MC3R agonist; NPY1 antagonist; NPY4 agonist; NPY5 antagonist; leptin; leptin agonist/modulator; leptin derivatives; opioid antagonist; orexin antagonist; BRS3 agonist; 11β HSD-1 inhibitor; CCK-A agonist; CNTF; CNTF agonist/modulator; CNTF derivative; Cox-2 inhibitor; GHS agonist; 5HT2C agonist; 5HT6 antagonist; monoamine reuptake inhibitor; UCP-1, 2, and 3 activator; β3 agonist; thyroid hormone β agonist; PDE inhibitor; FAS inhibitor; DGAT1 inhibitor; DGAT2 inhibitor; ACC2 inhibitor; glucocorticoid antagonist; acyl-estrogens; lipase inhibitor; fatty acid transporter inhibitor; dicarboxylate transporter inhibitor; glucose transporter inhibitor; serotonin reuptake inhibitors; aminorex; amphechloral; amphetamine; axokine; benzphetamine; chlorphentermine; clobenzorex; cloforex; clominorex; clortermine; cyclexedrine; dextroamphetamine; diphemethoxidine,N-ethylamphetamine;fenbutrazate; fenisorex;fenproporex; fludorex;fluminorex; furfurylmethylamphetamine; levamfetamine; levophacetoperane; mefenorex;metamfepramone; methamphetamine; nalmefene; norpseudoephedrine; pentorex; phendimetrazine; phenmetrazine; phytopharm compound 57; picilorex;topiramate; zonisamide; or a combination thereof.

11. Use of a cathepsin K inhibitor in the manufacture of a medicament for treating an obesity related disorder, preventing weight regain or for weight maintenance.

12. Use according to Claim 11, wherein said cathepsin K inhibitor is as defined in any one of Claims 2 to 4.

13. Use according to Claim 11 or 12, wherein the obesity related disorder is as defined in Claim 5.

14. A cathepsin K inhibitor for use in treating an obesity related disorder, preventing weight regain or for weight maintenance.

15. A cathepsin K inhibitor according to Claim 14, as defined in Claim 2, 3 or 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000054

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 1-8

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 1-8 are methods of medical treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. (Rule 39.1(iv) PCT) Regardless, this Authority has carried out a search based on the alleged effects of the cathepsin K inhibitors for the treatment of obesity, treatment of obesity related disorders, preventing weight gain, preventing weight regain or for weight maintenance.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000054

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/275*** (2006.01) , ***A61P 3/04*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/275 (2006.01) , ***A61P 3/04*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Delphion, PubMed, USPTO, Google™ (cathepsin K inhibitor/modulator/antagonist, cathepsin O inhibitor/modulator/antagonist, cathepsin O_2 inhibitor/modulator/antagonist, cathepsin X inhibitor/modulator/antagonist, cysteine protease inhibitor/modulator/antagonist, obesity, weight gain, weight maintenance, diabetes, arthritis, vascular disease, atherosclerosis, cancer, heart disease, leukemia, anti-obesity agent, anti-diabetic agent)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/24460 A2 (NOVARTIS-ERFINDUNGEN) 20 May 1999 see whole document	1, 4-15
X	WO 03/075836 A2 (MERCK FROSST CANADA & CO) 18 September 2003 see whole document	1-3, 5-15
X	WO 2005/000800 A1 (MERCK FROSST CANADA & CO) 06 January 2005 see whole document	1, 5-11, 13-14
X	WO 03/086325 A2 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC.) 23 October 2003 see whole document	1, 5-11, 13-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2006 (28-02-2006)	26 April 2006 (26-04-2006)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Tania Nish (819) 934-3592

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000054

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 483 998 A1 (ONO PHARMACEUTICAL CO, LTD) 06 November 2003 see whole document	1, 5-11, 13-14
X	CA 2 266 849 A1 (SYNPHAR LABORATORIES) 26 March 1998 see whole document	1, 5-11, 13-14
X	WO 02/100849 A2 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC.) 19 December 2002 see whole document	1, 5, 11, 13-14
P, X	WO 2005/019161 A1 (MERCK FROSST CANADA & CO) 03 March 2005 see whole document	1-3, 5-15
P, X	WO 2005/021487 A1 (MERCK FROSST CANADA & CO) 10 March 2005 see whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2006/000054

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO9924460		AU751669 B2	22-08-2002
		AU1487399 A	31-05-1999
		BR9813197 A	29-08-2000
		CA2306313 A1	20-05-1999
		CN1278244 A	27-12-2000
		EP1028942 A2	23-08-2000
		GB9723407D D0	07-01-1998
		HU0004400 A2	29-04-2002
		ID24931 A	31-08-2000
		IL135508D D0	20-05-2001
		JP2001522862T T	20-11-2001
		NO20002320 A	04-07-2000
		NZ503889 A	26-07-2002
		PL340819 A1	26-02-2001
		SK6572000 A3	09-10-2000
		TR200001189T T2	21-09-2000
		TW527362 B	11-04-2003
		US6353017 B1	05-03-2002
		US2004029814 A1	12-02-2004
		US2004110806 A1	10-06-2004
		ZA9810073 A	05-05-1999
WO03075836	18-09-2003	AU2003219953 A1	22-09-2003
		BR0308208 A	11-01-2005
		CA2477657 A1	18-09-2003
		CN1638757 A	13-07-2005
		EP1482924 A2	08-12-2004
		HR20040800 A2	30-04-2005
		JP2005526753T T	08-09-2005
		MA27295 A1	02-05-2005
		MXPA04008621 A	06-12-2004
		NO20044207 A	24-11-2004
		PL372204 A1	11-07-2005
		RU2004129587 A	10-05-2005
		US2003232863 A1	18-12-2003
		US2005240023 A1	27-10-2005
WO2005000800	06-01-2005	CA2530068 A1	06-01-2005
WO03086325	23-10-2003	AU2003230772 A1	27-10-2003
		CA2477692 A1	23-10-2003
		EP1495009 A2	12-01-2005
		JP2005522489T T	28-07-2005
		US6878706 B1	12-04-2005
CA2483998	06-11-2003	AU2003235118 A1	10-11-2003
		BR0309670 A	15-03-2005
		CN1649831 A	03-08-2005
		EP1498411 A1	19-01-2005
		MXPA04010523 A	08-06-2005
		NO20045137 A	25-11-2004
		RU2004134561 A	20-07-2005
		WO03091202 A1	06-11-2003
		ZA200409502 A	15-08-2005

CA2266849	26-03-1998	AU718918 B2	20-04-2000
		AU4133597 A	14-04-1998
		DE69719344D D1	03-04-2003
		DE69719344T T2	30-10-2003
		EP0929571 A1	21-07-1999
		JP2001501193T T	30-01-2001
		US5916887 A	29-06-1999
		US6034077 A	07-03-2000
		WO9812210 A1	26-03-1998
WO02100849	19-12-2002	CA2449192 A1	19-12-2002
		EP1399431 A2	24-03-2004
		JP2005501017T T	13-01-2005
		MXPA03011113 A	19-03-2004
		US6982263 B2	03-01-2006
WO2005019161	03-03-2005	NONE	
WO2005021487	10-03-2005	NONE	