Therapeutic Agents

This invention relates to a method for treating obesity and associated co-morbid conditions and to products and pharmaceutical compositions suitable for use in such a method. More particularly, the invention relates to a method for the treatment of obesity and associated co-morbid conditions by the administration of sibutramine or a salt or a metabolite thereof and a lipase inhibitor and to products and compositions containing such compounds.

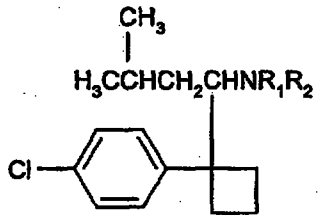
Sibutramine is a 5-hydroxytryptamine and noradrenaline reuptake inhibitor *in vivo* (Buckett, W.R., Thomas, P.C. & Luscombe, G.P. (1988). Prog. Neuro-Psychopharmacol. Biol. Psychiat. 12, 575-584 and Luscombe, G.P., Hopcroft, R.H., Thomas, P.C. & Buckett, W.R. (1989). Neuropharmacology, 28, 129-134.) Studies have shown that it reduces body weight by a dual mode of action; it decreases food intake by enhancing satiety (Fantino, M. & Souquet, A.-M. (1995). Int. J. Obesity, 19, 145; Halford, J.C.G., Heal, D.J. & Blundell, J.E. (1995). Brit. J. Pharmacol. 114, 387P; and Stricker-Krongrad, A., Souquet, A.-M. & Burlet, C. (1995). Int. J. Obesity, 19, 145.), and it increases energy expenditure by stimulating thermogenesis (Connoley, I.P., Heal, D.J. & Stock, M J. (1995). Brit. J. Pharmacol. 114, 388P; and Connoley, I P., Frost, I., Heal, D.J. & Stock, M.J. (1996). Brit. J. Pharmacol. 117, 170P). Sibutramine has been approved for use in the treatment of obesity in the USA and at least twenty other countries worldwide.

Lipase enzymes are responsible for breaking down ingested fat (Borgstrom, B. (1988). Biochem. Biophys. Acta. 962 (3), 308-316); as a consequence of this, unabsorbed fat is egested in the faeces. One such lipase inhibitor, orlistat, which has now been approved for use in the treatment of obesity in the USA and Europe, has the chemical name (2*S*, 3*S*, 5*S*)-5-[(*S*)-2-formamido-4-methylvaleryloxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone. It is also known as "N-formyl-L-leucine, ester with (3*S*, 4*S*)-3-hexyl-4-[(2*S*)-2-hydroxy-tridecyl]-2-oxetanone", (-)-tetrahydrolipstatin, tetrahydrolipistatin, and orlistat. The extraction and use of orlistat in the control or prevention of obesity and hyperlipaemia is described in US Patent 4598089 (Hoffmann-La Roche Inc.). A process for the preparation of orlistat is described in

US Patent 4983746 (Hoffmann-La Roche Inc.). A composition comprising orlistat and acarbose is described in EP638317 (Hoffmann-La Roche AGF).

It has been reported that orlistat should not be combined with appetite suppressants (The New York Times May 15 1997) . Co-pending application PCT/EP98/08249 discloses the use of a combination of a compound of formula I as described below and orlistat in the treatment of obesity. Surprisingly, it has now been found that co-administration of sibutramine hydrochloride monohydrate and a lipase inhibitor results in beneficial effects with respect to weight-loss.

Accordingly, the present invention provides a method for the treatment of obesity and associated co-morbid conditions in a mammal in need of such treatment, particularly a human, which comprises administration to the mammal in need thereof, particularly a human, of a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a lipase inhibitor with the proviso that the lipase inhibitor is not orlistat;
wherein the compound of formula I and the lipase inhibitor are administered simultaneously, separately or sequentially.

The present invention may provide the following advantages. Firstly, the maximum weight loss achieved is greater than that achieved by the sole administration of either a compound of formula I or of a lipase inhibitor. Secondly, a synergistic weight loss is achieved in which the weight loss obtained by the administration of a compound of formula I and a lipase inhibitor to a first test group is greater than the total weight loss achieved by administration of the compound of formula I to a second test group and the weight loss achieved by administration of a lipase inhibitor to a third test group. Thirdly, when weight loss has reached a plateau after administration of either a compound of formula I or a lipase inhibitor, a further weight loss is achieved by administering the other compound. Fourthly, lower doses

of the compound of formula I and the lipase inhibitor may be used in the present invention thus reducing the side-effects associated with administration of a higher dose of each compound. Fifthly a synergistic improvement in the treatment of the co-morbid conditions associated with obesity may be achieved with the present invention compared to the sole adminstration of each compound.

A preferred compound of formula I is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine or a salt thereof, for example the hydrochloride salt, known as sibutramine hydrochloride. A preferred form of this hydrochloride is its monohydrate, known as sibutramine hydrochloride monohydrate.

The preparation and use of compounds of formula I, such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride in the treatment of obesity is described in European Patent Number 397831. A particularly preferred form of this compound N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate (sibutramine hydrochloride monohydrate) which is described in European Patent Number 230742. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of

diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Enantiomers of secondary and tertiary amines of formula I can also be prepared by preparing the primary amine racemate, resolving this mixture into its individual enantiomers and then converting the relevant optically pure primary amine enantiomer into the desired secondary or tertiary amine product.

Preferred compounds of formula I are N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine, and N-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof. Specific enantiomers of formula I are (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (R)-(+)-N-{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}-N-methylamine, (S)-(-)-N-{1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutyl}-N-methylamine, (R)-(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and (S)-(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

Suitable lipase inhibitors include pancreatic lipase inhibitors, gastric lipase inhibitors and carboxylester lipase inhibitors and include but are not limited to the following:

caulerpenin as described in patent no. JP10203974A2, application no. 97JP-0014334;

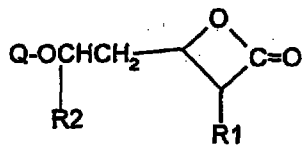
panclicins A-E , as described in J. Chem. Soc., Perkin Trans. 1 (1998), (8), 1373-1382;

(-)-panclicin D, as described in Tetrahedron (1997), 53(48), 16471-16488;

procyanidin and analogues as described in WO9723210;

lipase inhibitors isolated from cereal or legume as described in patent no. JP04321700A2 application no.91JP-0110814;

4-(acyloxyethyl)oxetan-2-ones of formula



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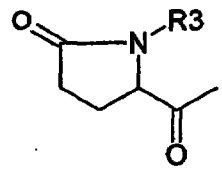
as described in EP-444482 wherein Q is a group of the formula

$(R_3,R_4)NCO(X)_n$-CO- Q_1

$(R_3,R_4)NCO$-X_1 Q_2



Q_3

and

R_1 and R_2 are alkyl with up to 18C atoms substituted by 1 to 3 halogen atoms or alkyl, alkenyl, alkynyl or alkadienyl groups with up to 20 C atoms optionally interrupted by a 1,4-arylene group, optionally substituted by an aryl group in the omega–position and optionally substituted by an aryl-C_{1-4}-alkyl group; whereby R_1 can be interrupted by an O or S atom or by a sulphinyl or sulphonyl group in a position other than the α-position to an unsaturated C atom, or R_1 is an aryl-NH- or aryl-C_{1-4}-alkyl-OCONH-group,

R_3 and R_4 are hydrogen or C_{1-4}-alkyl or together with the N atom to which they are attached form a saturated 3-to 6-membered ring optionally containing an O or S atom in a position other than the α-position to the N atom,

n is the number 1 or 0

X is an alkylene group, which contains up to 6 C atoms, which is optionally interrupted by an O or S atom or by a sulphinyl or sulphonyl group and which is optionally substituted by a hydroxy, mercapto, aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl-C_{1-4}-alkoxy, aryl-C_{1-4}-alkylthio, aryl-C_{1-4}-alkylidene, C_{3-7}-cycloalkylidene or C_{1-6}-alkylidene group or by one or two C_{1-6}-alkyl, C_{1-6}-alkoxy or C_{1-6}alkylthio groups, whereby two C_{1-6}alkyl, C_{1-6}-alkoxy or C_{1-6}-alkylthio groups on the same C atom or on two adjacent C atoms can form an optionally mono-unsatured 3- to 7-membered ring and an optionally present hydroxy or mercapto group or an optionally present unsaturated C atom must be in a position other than the α-position to an optionally present O or S atom or to an optionally present sulphinyl or sulphonyl group, or

X is a group of the formula

$$=CHN(R,R^0) \text{ or } -CHN(R,R^0)CH_2-$$

R and R^0 are hydrogen, C_{1-4}-alkyl, C_{1-4}-alkyl(CO or OCO)-, aryl, aryl(CO or OCO)-, aryl-C_{1-4}-alkyl or aryl-C_{1-4}-alkyl(CO or OCO)- and

X_1 is an alkylene group containing up to 6 C atoms which can be substituted by a C_{1-4}-alkoxy, aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl- C_{1-4}-alkoxy or aryl- C_{1-4}-alkylthio group or by one or two C_{1-6}-alkyl groups, whereby two C_{1-6}-alkyl groups, attached to adjacent C atoms can form a 3- to 7-membered ring; particularly a compound selected from:

(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (S)-2-isopropylmalonamate,
(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (S or R)-2-carbamoyl-valerate,
(all Z,S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxytanyl]methyl]9,12-octadecadienyl (S)-2-isopropylmalonamate,
(S)-1-[[(2S,3S or 2R,3R)-4-oxo-3-pentylthio-2-oxetanyl]methyl]dodecyl (S)-2-isopropylmalonamate,
(S)-1-[[(2S,3S or 2R,3R)-4-oxo-3-pentylthio-2-oxetanyl]methyl]dodecyl [S:R(2:1)-2-isopropylmalonamate,
(S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]-methyl]octadecyl (S or R)-2-t-butyl-malonamate
(S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl 1-carbamoylcyclo-pentanecarboxylate,
(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (RS)-2-benzylmalonamate,
(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (3-[(2-carbamoylethyl)thio]-propionate,
5-oxo-D-proline (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester,
5-oxo-L-proline (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester,

(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (S or R)-2-isopropyl-malonamate,
(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (RS)-2-carbamoylvalerate (epimers 1:1),
(all Z,S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxytanyl]methyl]9,12-octadecadienyl (S or R)-2-isopropylmalonamate,
(S)-1-[[(2S,3S)-3 hexyl-4-oxo-2-oxetanyl]methyl]dodecyl (RS)-2-carbamoyl-4-methyl-valerate (epimers 1:1),

(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl 1-carbamoylcyclohexane-carboxylate,

(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl [RS)-2-methylmalonamate, (epimers 1:1),

(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl [RS)-2-ethylmalonamate, (epimers 1:1),

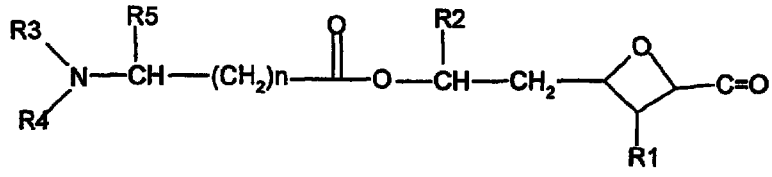
(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl [RS)-2-butylmalonamate, (epimers 1:1),

(S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl 1-carbamoylcyclo-hexanecarboxylate,

S)-1-[[(2S,3S or 2R,3R)-4-oxo-3-penylthio-2-oxetanyl]methyl]dodecyl [S:R or R:S (2:1)-2-isopropylmalonamate,

(S)-1-[[(2R,3R)-3-benzyl-4-oxo-2-oxetanyl]methyl]dodecyl [S or R)-2-isopropyl-malonamate;

N-formylleucine 1-(oxetanonylmethyl)alkyl esters and analogs as described in US4931463, US5175186 and US5246960 of formula



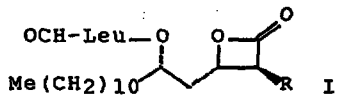
wherein R_1 and R_2 are independently C_{1-17} alkyl which is saturated or optionally interrupted by up to 8 double or triple bonds and/or optionally interrupted by an O or S atom which is present in a position other than the α–position to an unsaturated C-atom; or phenyl, benzyl or $-C_6H_4$-X- C_6H_5 ring-substituted by up to 3 C_{1-6}-alkyl-(O or S) $_{1 \text{ or } 0}$ groups, X is oxygen, sulfur or $(CH_2)_{0-3}$, R_3 is hydrogen, C_{1-3}-alkyl or C_{1-3} alkanoyl, R_4 is hydrogen or C_{1-3}-alkyl, and R_5 is hydrogen, a group Ar or Ar-C_{1-3}alkyl or C_{1-7}-alkyl optionally interrupted by Y and optionally substituted by Z, or R_4 forms with R_5 a 4- to 6-membered saturated ring, Y is oxygen, sulfur or a group $N(R_6)$, $C(O)N(R_6)$ or $N(R_6)C(O)$, Z is a group –(O or S)-R_7, -$N(R_7,R_8)$, -$C(O)N(R_7,R_8)$ or

-N(R_7)C(O)R_8, n is the number 1 or 0, with the proviso that R_5 is hydrogen when n is the number 1, Ar is phenyl which is unsubstituted or substituted by up to 3 groups R_9 or OR_9, and R_6, R_7, R_8 and R_9 individually are hydrogen or C_{1-3}-alkyl, with the proviso that R_4 is other than hydrogen when R_3 is formyl and R_5 is isobutyl or R_3 is acetyl and R_5 is carbamoylmethyl, and simultaneously R_2 is undecyl or 2,5-undecadienyl and R_1 is n-hexyl, an enantiomer or a diastereomer thereof, or a pharmaceutically acceptable acid addition salt thereof particularly a compound selected from one of the following:

N-formyl-(S)-leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester, or a pharmaceutically acceptable acid addition salt thereof, particularly:

N-formyl-L-leucine 1-[(trans-3-ethyl-4-oxo-2-oxetanyl)methyl]dodecyl ester
N-formyl-L-leucine 1-[(trans-3-allyl-4-oxo-2-oxetanyl)methyl]dodecyl ester
N-formyl-S-leucine (S,9Z,12Z)-1[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9,12-octadecadienyl ester
N-formyl-S-leucine (S, Z)-1[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9-octadecenyl ester
N-formyl-S-leucine (R)-α-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-p-phenoxy-benzyl ester;
or a pharmaceutically acceptable acid addition salt thereof;

a tetrahydrolipstatin analog of formula in which R = ethyl I Helv.Chim. Acta (1987), 70(5), 1412-18



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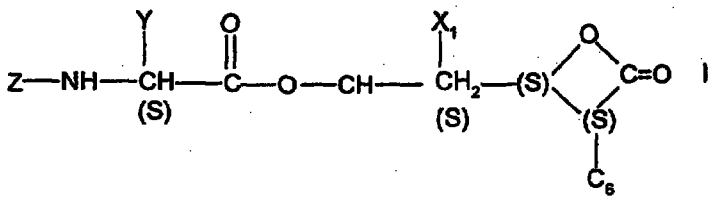
oxetanones of formula



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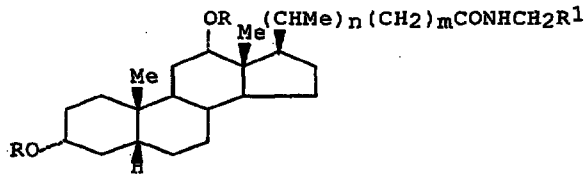
wherein X^1 is undecyl or 2Z,5Z-undecadiencyl, C_6 is n-hexyl, Y is isobutyl and Z is formyl or Y is carbamoylmethy and Z is acetyl

] as described in EP-189577

1-substituted 2-alkanone derivatives as described in Chem. Pharm. Bull. (1986), 34(3), 1118-27;

soybean proteins as described in J. Lipid Res. (1984), 25(11), 1214-21;

taurine and glycine derivatives of formula



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in which R = H, alkanoyloxy, BzO; R1 = CO2H, alkoxycarbonyl, CH2SO3H; m, n = 0, 1) as described in US4104285;

1,2-dioleoyl-3-(.alpha.-1-adamantoyl)-sn-glycerol and 1-adamantanecarboxylic acid as described in J. Pharm. Sci. (1976), 65(8), 1243-5;

peptides derived from wheat as described in JP07330794 A;

peptides incorporating a C-terminal fragment of pancreatic lipase including a site for recognition of a co-lipase as described in WO9830588;

flavanoid(s) and their glycoside(s) as described in JP09143070A;

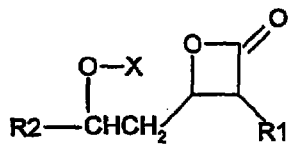
tri-terpenes as described in JP09040689A;

hinokitiol as described in JP08268882A;

flavonoid compounds as described in JP07061927A;

(metal substd.) chlorophyllin(s) as described in JP05252898 A;

2-oxetanone derivatives of formula I as described in EP443449A:



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wherein

R_1 and R_2	are alkyl with up to 17C atoms optionally interrupted by an O atom in a position other than the α-or β-position; or benzyl optionally ring-substituted by 1 to 3 C_{1-6}-alkyl or C_{1-6}-alkoxy groups,
X	is hydrogen or a group of the formula $(R_3,R_4)NCH(R_5)(CH_2)_n$-CO-
R_3	is hydrogen, C_{1-3}-alkyl or C_{1-3}-alkanoyl,
R_4	is hydrogen or C_{1-3}-alkyl and
R_5	is hydrogen, a group Ar or Ar-C_{1-3}-alkyl or C_{1-7}-alkyl optionally interrupted by Y and optionally substituted by Z or
R_4 with R_5	form together with the N atom to which they are attached a 4- to 6-membered ring,
Y	is oxygen, sulphur or a group $N(R_6)$, C(O) $N(R_6)$ or $N(R_6)C(O)$,
Z	is a group –(O or S)-R_7, NR_7,R_8) or $N(R_7)C(O)R_8$,
n	is the number 1 or 0, whereby R_5 is hydrogen when n is the number 1,
Ar	is phenyl substituted by 1 to 3 groups R_9 or OR_9,
	and
R_6 to R_9	are hydrogen or C_{1-3}-alkyl,

and of salts of the oxetanones of formula I in which X is not hydrogen with weak acids;

lipstatin and tetrahydro lipstatin derivatives as described in EP129748A with the exception of orlistat;

non-absorbable cationic deriv. of olefin -maleic acid copolymers described in US4211765A;

bile acid and triglyceride absorbing resins as described in GB1286949; and compounds such as ATL-962 and analogues thereof as described in patent applications covering this compound and patent applications covering analogues thereof.

In the method of the present invention a compound of formula I and a lipase inhibitor may be administered concomitantly or concurrently, for example in the form of separate dosage units to be used simultaneously, separately or sequentially.

In another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

In yet another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat as a combined preparation for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

In a further aspect the present invention provides a product containing a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat as a combined preparation for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

In yet another aspect the present invention provides the use of a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament

for the treatment of obesity and associated co-morbid conditions in a patient who is also receiving treatment with a lipase inhibitor with the exception of orlistat.

In a further aspect, the present invention provides a method of treating obesity and associated co-morbid conditions comprising the administration of an adjunctive therapy comprising a therapeutically effective amount of a compound of formula I and a lipase inhibitor with the exception of orlistat to a patient in need thereof.

The invention also provides the use of the above combination of drugs in the manufacture of a medicament for the treatment of obesity and associated co-morbid conditions. Additionally, it provides the combination for use in the treatment of obesity.

The term "associated co-morbid conditions" as used in this document means medical conditions known to those skilled in the art to be associated with obesity. The term includes but is not limited to the following: diabetes including non-insulin dependent diabetes mellitus, impaired glucose tolerance, depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, hyperglycaemia, hyperlipidaemia, and stress in mammals particularly humans.

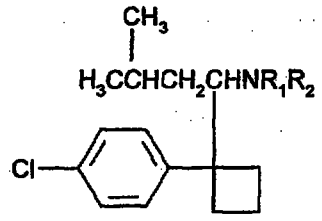
In addition the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for example non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence including stress incontinence, hyperactivity disorders, hiatial hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

The present invention may be useful in preventing cardiovascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy, in reducing the craving to smoke and in aiding weight loss after smoking cessation. The present invention may also be useful in lowering uric acid levels and lipid levels in mammals particularly humans.

The amount of each compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound of formula I to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses and more preferably 10 mg, 15 mg, 20 mg, 25 mg or 30 mg per day and most preferably 20 mg. The dosage of the lipase inhibitor to be administered will be in the range of 5 to 2000 mg given in one or more doses, preferably three times daily, more preferably in the range of 50 to 1500 mg and most preferably in the range of 100 to 1000 mg . The compound of formula I, preferably sibutramine hydrochloride monohydrate, may be administered in any of the known pharmaceutical dosage forms. The lipase inhibitor is preferably administered orally.

In a preferred aspect of the present invention sibutramine hydrochloride monohydrate is administered once daily, preferably first thing in the morning, and the lipase inhibitor is administered three times daily either with or before meals. Preferably the dose of sibutramine hydrochloride monohydrate is 20 mg or 30 mg administered once daily and the dose of the lipase inhibitor is 50 mg, 100 mg, 120 mg, or 150 mg administered three times daily either with or before meals. Most preferably the dose of sibutramine hydrochloride monohydrate is given prior to the first dose of the lipase inhibitor, preferably in the range of 30 minutes to 3 hours, for example 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours, before the first dose of the lipase inhibitor.

In another aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a lipase inhibitor with the exception of orlistat in conjunction with a pharmaceutically acceptable diluent or carrier.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compounds with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the compound of formula I and 1 to 1000 mg of the lipase inhibitor.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compounds in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose, and oily suspensions containing the active compounds in a suitable vegetable oil, for

example arachis oil. The active compounds may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compounds are administered through the mucosa of the mouth.

Dosage forms of the compounds of formula I suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms of the compounds of formula I suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms of the compounds of formula I for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of each active compound contained in a topical formulation should be such that a therapeutically effective amount of each compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be

administered from a pump pack or from a pressurised pack containing a volatile propellant.

The compound of formula I may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compounds to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compounds to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compounds to be infused. The support may be a single body containing all the compounds or a series of several bodies each containing part of the compounds to be delivered. The amount of active compounds present in an internal source should be such that a therapeutically effective amount of each compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compounds may, if desired, be associated with other compatible pharmacologically active ingredients. Optionally vitamin supplements may be administered with the compounds of the present invention.

Pharmaceutical compositions incorporating both a compound of formula I and a lipase inhibitor are important embodiments of the present invention. Such pharmaceutical compositions contain a therapeutically effective amount of each of the compounds. Each dosage unit may contain the daily doses of both compounds, or may contain a fraction of the daily dose, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case, the patient would

daily take one of the combination dosage units, and one or more units containing only the other compound.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes either or both compounds of the invention unless otherwise stated.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories (Compound of formula I only)

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Sibutramine hydrochloride monohydrate	20
Lipase Inhibitor	50, 100, 120 or 150
Starch	200
Magnesium stearate	10
Total	350

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Sibutramine hydrochloride monohydrate	10
Lipase Inhibitor	50, 100, 120 or 150
Microcrystalline Cellulose	400
Silica	10

	Quantity (mg/tablet)
Stearic acid	5
Total	545

The components are blended and compressed to form tablets.

The advantages of the present invention may be demonstrated by one or more of the following studies

Study 1

Groups of normal adult male Sprague-Dawley CD rats (n = 8-12) receive the following treatments

a) Group 1; daily dosing with sibutramine hydrochloride monohydrate (1, 3 or 10 mg/kg po) plus the lipase inhibitor vehicle po.

b) Group 2; bidaily dosing of a lipase inhibitor po (for example 10, 20, 30, 40, 50, 100 or 150 mg/kg po preferably 10 or 20 mg/kg) plus sibutramine vehicle po.

c) Group 3; combined po treatment with doses of sibutramine hydrochloride monohydrate and a lipase inhibitor.

d) Group 4; control, dosed po with the sibutramine and the lipase inhibitor vehicles.

The rats are allowed free access to high-fat diet. Food intake, water intake and body-weight are measured daily and the duration of treatment is 15, 21 or 28 days.

Study 2

Groups of obese female Zucker rats (n = 8-12) maintained on a high-fat diet receive the following treatments

a) Group 1; daily po dosing with sibutramine hydrochloride monohydrate for 14 days at a dose which significantly reduces body weight compared to vehicle-treated controls (1, 3 or 10 mg/kg po). Daily treatment for the next 14 days is with an identical dose of sibutramine hydrochloride monohydrate po plus a

dose of a lipase inhibitor (for example 10, 20, 30, 40, 50, 100 or 150 mg/kg po preferably 10 or 20 mg/kg).

b) Group 2; daily dosing with sibutramine hydrochloride monohydrate po for 14 days. Daily treatment for the next 14 days with sibutramine po and the lipase inhibitor vehicle po.

c) Group 3; daily dosing with sibutramine hydrochloride monohydrate vehicle po for 14 days followed by combined treatment with sibutramine hydrochloride monohydrate vehicle po and the lipase inhibitor vehicle po for the following 14 days.

Study 3

Groups of normal adult male Sprague-Dawley CD rats (n=8-12) receive the following treatments:-

a) Group 1; dosing with sibutramine hydrochloride monohydrate (1, 3 or 10 mg/kg po) plus lipase inhibitor vehicle po

b) Group 2; dosing with lipase inhibitor po plus sibutramine vehicle po

c) Group 3; dosing with lipase inhibitor po plus sibutramine vehicle po

d) Group 4; dosing with lipase inhibitor vehicle po plus sibutramine vehicle po

Sibutramine is dosed once daily, the lipase inhibitors are administered (in a suitable dose) up to three times a day. Groups 1, 3 and 4 have free access to a high-fat diet at all times. Group 2 is pair-fed with the sibutramine-treated group (Group 1), i.e. the animals are given the amount of food (high-fat diet) eaten by the sibutramine-treated group over the previous 24 h period. Food intakes and body weights are measured daily and the duration of treatment is 4-5 days.

A statistical comparison between the body weights of animals in each group in one or more of the above studies provides results demonstrating the advantage of the present invention.

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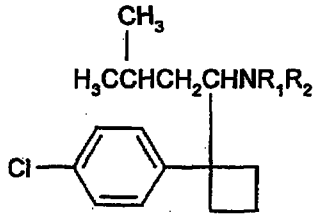
Claims

1) A method for the treatment of obesity and associated co-morbid conditions in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a lipase inhibitor with the exception of orlistat;
wherein the compound of formula I and are administered simultaneously, separately or sequentially.

2) A method according to claim 1 in which the compound of formula I is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine or a salt thereof.

3) A method according to claim 2 wherein the compound of formula I is administered 30 minutes to 3 hours prior to the administration of the lipase inhibitor.

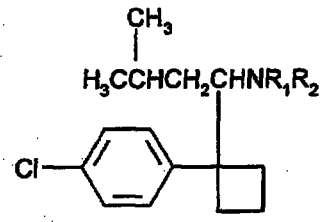
4) A compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat;
for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

5) A compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat;
as a combined preparation for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

6) A product containing a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and a lipase inhibitor with the exception of orlistat;
as a combined preparation for simultaneous, separate or sequential use for the treatment of obesity and associated co-morbid conditions.

7) The use of a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament for the treatment of obesity and associated co-morbid conditions in a patient who is also receiving treatment with a lipase inhibitor with the exception of orlistat.

8) A pharmaceutical composition comprising a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a lipase inhibitor with the exception of orlistat.