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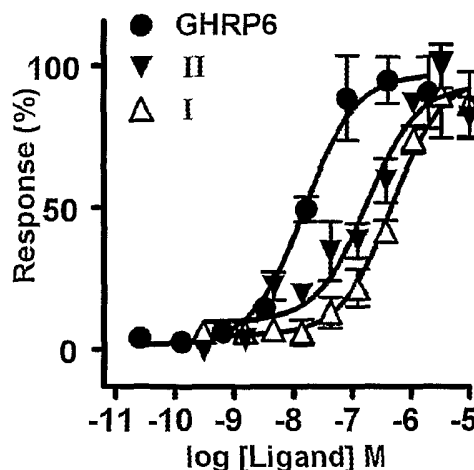
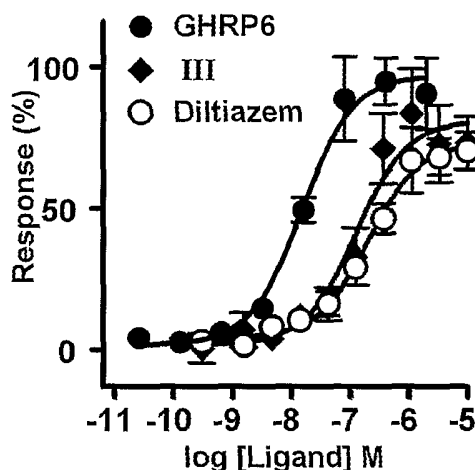
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(54) Title: COMPOUNDS AS MODULATORS OF GHRELIN RECEPTOR AND USES THEREOF



(57) Abstract: Disclosed herein are compounds of Formula (I) as defined herein, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, that selectively activate the ghrelin receptor, and pharmaceutical compositions comprising the same. Disclosed herein are also methods of treatment of diseases and disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I).

COMPOUNDS AS MODULATORS OF GHRELIN RECEPTOR AND USES THEREOF

RELATED APPLICATIONS

[0001] The present application claims priority to the U.S. Provisional Application Serial No. 60/645,669, filed on January 20, 2005, by Olsson et al., and entitled "COMPOUNDS AS MODULATORS OF GHRELIN RECEPTOR AND USES THEREOF," the entire disclosure of which is hereby incorporated by reference herein, including any drawings.

FIELD OF INVENTION

[0002] The present invention relates to the discovery of benzothiazepin compounds as potent Ghrelin receptor (GHSR1a) agonists for the treatment of eating disorders, hormone insufficiencies, dwarfism; somatopause, osteoporosis, wasting syndromes, catabolic states, cardiovascular diseases, gastro-intestinal diseases, sleep disorders, cancers; agricultural uses such as the production of meat, milk, fish and eggs; for disorders of the pancreas, diabetes, anxiety disorders and cognitive deficits, and for diagnosing hormone insufficiencies.

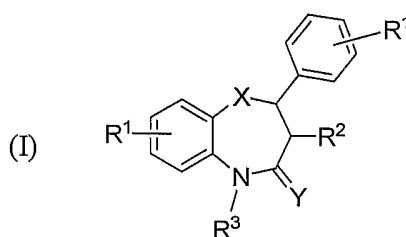
BACKGROUND OF THE INVENTION

[0003] The physiological actions of the hormone/neurotransmitter ghrelin are mediated, in part, by the ghrelin receptor. The ghrelin receptor is expressed in a number of tissues including the pituitary and hypothalamus, as well as other brain regions such as hippocampus, as well as peripheral tissues such as heart, lung, pancreas, stomach, intestine, and adipose tissue and numerous other tissues where it is thought to regulate appetite, energy balance, cardiovascular function, gastrointestinal motility, hormone release, induction of slow wave sleep, and cellular proliferation (1-4). Compounds that stimulate ghrelin receptors have been shown to stimulate appetite and food intake, improve cardiac output and reduce cardiac afterload, stimulate gastric motility and emptying, facilitate induction of sleep, and inhibit cellular proliferation in cells derived from the lung, thyroid and breast whereas compounds

that block ghrelin receptor activity have been shown to reduce appetite and food intake (1-4). Thus there is potential clinical utility for compounds that modulate the activity of ghrelin receptors.

SUMMARY OF THE INVENTION

[0004] Disclosed herein are compounds of Formula I



as defined herein, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, that selectively activate the ghrelin receptor.

[0005] Disclosed herein are also methods of treatment of diseases and disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Figure 1 is a graph showing the agonist activity of diltiazem and diltiazem analogs of Formula I at ghrelin receptors in R-SAT assays.

[0007] Figure 2 is a graph showing the agonist activity of diltiazem and diltiazem analogs of Formula I at ghrelin receptors in phosphatidyl inositol hydrolysis assays

[0008] Figure 3 is a graph showing the growth hormone release in freely moving male Sprague-Dawley rats following intraperitoneal administration of diltiazem and a diltiazem analog of Formula I

[0009] Figure 4 is a graph showing the agonist activity of diltiazem and diltiazem analogs of Formula I in Ca²⁺ mobilization assays.

[0010] Figure 5 is a graph showing the reversal of carageenan-induced edema in the paw of Sprague-Dawley rats following intraperitoneal administration of diltiazem and a diltiazem analog of Formula I.

[0011] Figure 6 is a graph showing the stimulation of food intake in Sprague-Dawley rats following intraperitoneal administration of diltiazem and a diltiazem analog of Formula I.

DETAILED DISCLOSURE OF THE INVENTION

[0012] Surprisingly, it has been found that the Ca^{2+} channel blocking compound diltiazem (CAS registry number 33286-22-5) possesses heretofore unappreciated potent agonist activity at the human ghrelin receptor. We further demonstrate that diltiazem stimulates growth hormone release in rats. These observations have practical applications that support the use of diltiazem. Furthermore, analogs of diltiazem, including metabolites of diltiazem (henceforth collectively referred to as diltiazem analogs of formula I) are shown to have potent agonist activity at the human Ghrelin receptor. The molecular activities of diltiazem, or diltiazem analogs of formula I, as identified by the present methods, indicate that diltiazem, or diltiazem analogs of formula I can be used to alleviate or treat disorders or conditions affected directly or indirectly through ghrelin receptors.

[0013] We have profiled a large series of drugs that have utility in treating human disease for functional activity at the Ghrelin receptor and discovered that diltiazem and analogs of formula I displays robust ghrelin receptor agonist activity.

[0014] Thus, in a first aspect, the present invention relates to the use of diltiazem, or diltiazem analogs of formula I in animal subjects, for the production of food, such as, for example, meat, milk, eggs or fish. This aspect of the present invention also relates to a method of increasing food production comprising administering to a subject, such as an animal raised for food production, a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I, for the purpose of increasing the production of meat, milk, eggs or fish.

[0015] In another aspect, the present invention relates to the use of diltiazem, or diltiazem analogs of formula I in human subjects, being useful in the treatment of a disease or disorder. This aspect of the present invention also relates to a method of treating a disease or disorder comprising identifying a subject in need thereof and administering to the subject a

therapeutically effective amount of diltiazem, or diltiazem analog, for the purpose of controlling the symptoms observed during these syndromes.

[0016] In some embodiments, the methods of the present invention relate to the treatment of eating disorders. Treatment of eating disorders can include controlling the symptoms observed during these syndromes, such as, for example, loss of appetite. Eating disorders treatable by the methods of the present invention include, but are not limited to, anorexia, bulimia, cachexia, and cancer cachexia.

[0017] In another embodiment, the methods of the present invention relate to the treatment of wasting disorders. Treatment of eating disorders can include controlling the symptoms observed during these syndromes such as loss of weight. Wasting disorders treatable by the methods of the present invention include, but are not limited to, wasting, wasting associated with AIDS, AIDS related cachexia, wasting associated with surgical stress, cachexia of critical illness, wasting associated with sepsis, wasting associated with glucocorticoid administration, wasting associated with cancer.

[0018] In another embodiment, the methods of the present invention relate to the promotion of weight gain. Promotion of weight gain can include reversing catabolic states.

[0019] In another embodiment, the methods of the present invention relate to the treatment of gastrointestinal disorders. Treatment of gastrointestinal disorders can include reversing the symptoms observed with these syndromes. Such symptoms can include loss of gastric motility. Gastrointestinal disorders treatable by the methods of the present invention include, but are not limited to, reduced gastric and intestinal motility, post-operative gastric ileus, delayed gastric emptying, delayed gastric emptying due to diabetes, delayed gastric emptying post-operatively, short bowel syndrome, and gastric ulcers.

[0020] In another embodiment, the methods of the present invention relate to the treatment of cardiovascular disorders. Treatment of cardiovascular disorders can include reversing the symptoms observed with these syndromes. Cardiovascular disorders treatable by the methods of the present invention include, but are not limited to, angina, cardiac ischemia, cardiac failure, hypertension, hypotension, and atherosclerosis. The methods of the present invention are also effective in reducing cardiac afterload and/or increasing cardiac output.

[0021] In another embodiment, the methods of the present invention relate to the treatment of sleep disorders. The methods of the present invention are also effective in the treatment of insomnia, narcolepsy, catalepsy, somnolence, daytime somnolence, in improving sleep architecture, in facilitating induction of sleep, and in improving the quality of sleep.

[0022] In another embodiment, the methods of the present invention relate to the treatment of cancer. The methods of the present invention are also effective in controlling unwanted cellular proliferation associated with cancer.

[0023] In another embodiment, the methods of the present invention relate to the diagnosis of hormone deficiencies. The methods of the present invention are also effective in diagnosis of deficiencies in producing growth hormone, ACTH, cortisol, insulin-like growth factor 1 (IGF-1), and prolactin. The methods of the present invention are also effective in stimulating hormone production.

[0024] In another embodiment, the methods of the present invention relate to the treatment of hormone deficiencies and associated disorders. Hormone deficiency disorders treatable by the methods of the present invention include, but are not limited to, deficiencies in producing growth hormone, ACTH, cortisol, insulin-like growth factor 1 (IGF-1), and prolactin.

[0025] In another embodiment, the methods of the present invention relate to the treatment of dwarfism, somatopause, catabolic states, and osteoporosis.

[0026] In another embodiment, the methods of the present invention relate to the treatment of disorders of the pancreas, diabetes, and control of glucose levels.

[0027] In another embodiment, the methods of the present invention relate to the treatment of anxiety disorders and cognitive deficits. The methods of the present invention are also effective in relieving symptoms of anxiety and improving memory.

[0028] In another embodiment, the methods of the present invention relate to the treatment of neurodegenerative disorders. In some embodiments, the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Amyotrophic Lateral Sclerosis (ALS) and multiple sclerosis.

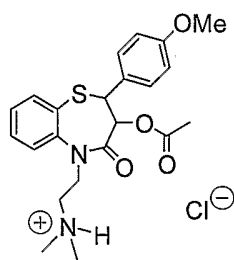
[0029] In another embodiment, the methods of the present invention relate to the treatment of inflammatory disorders including but not limited to rheumatoid arthritis, and atherosclerosis. The methods of the present invention are also effective in relieving the symptoms of inflammation.

[0030] In another embodiment, the methods of the present invention relate to the control of appetite, including but not limited to suppression of excessive food intake. The methods of the present invention are also effective in relieving the symptoms.

[0031] In some embodiments, the methods of the present invention relate to the treatment of eating disorders or disorders related to eating disorders. Treatment of eating disorders can include controlling the symptoms observed during these syndromes, such as, for example, increased appetite and binge eating. Disorders treatable by the methods of the present invention include, but are not limited to obesity, metabolic syndrome, appetite disorders, cachexia, anorexia, bulimia, high cholesterol and hyperlipidemia.

[0032] In another embodiment, the methods of the present invention relate to the promotion of weight loss. Promotion of weight loss can include reversing anabolic states.

[0033] Diltiazem, (+)-(2S,3S)-2,3-dihydro-3-acetoxy-2-(4-methoxyphenyl)-5-[2-(dimethylamino) ethyl]-1,5-benzothiazepin-4-(5H)-one hydrochloride, CAS registry number 33286-22-5, is defined as the compound whose molecular structure is shown in Formula II.



Formula II Chemical Structure of diltiazem

[0034] Throughout the present disclosure, the word "diltiazem" is not limited to the hydrochloride salt; instead the recitation of "diltiazem" includes any and all salts other than the hydrochloride salt. Further, the word "diltiazem" includes the free base compound. The scope of the present invention also includes the use of other diastereomers of diltiazem, including the (-) isomer, the (2R,3S) isomer, the (2S,3R) isomer, and the (2R,3R) isomer. The scope of the

present invention also includes the use of mixtures of any and all of the above isomers, including racemic and optically inactive mixtures.

[0035] An “agonist” is a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor), or a compound that increases the activity of a receptor when it contacts the receptor.

[0036] The term “antagonist” is defined as a compound that competes with an agonist or inverse agonist for binding to a receptor, thereby blocking the action of an agonist or inverse agonist on the receptor. However, an antagonist (also known as a “neutral” antagonist) has no effect on constitutive receptor activity.

[0037] The term “inverse agonist” is defined as a compound that decreases the basal activity of a receptor (i.e., signaling mediated by the receptor). Such compounds are also known as negative antagonists. An inverse agonist is a ligand for a receptor that causes the receptor to adopt an inactive state relative to a basal state occurring in the absence of any ligand. Thus, while an antagonist can inhibit the activity of an agonist, an inverse agonist is a ligand that can alter the conformation of the receptor in the absence of an agonist. The concept of an inverse agonist has been explored by Bond et al. in *Nature* 374:272 (1995). More specifically, Bond et al. have proposed that unliganded β_2 -adrenoceptor exists in an equilibrium between an inactive conformation and a spontaneously active conformation. Agonists are proposed to stabilize the receptor in an active conformation. Conversely, inverse agonists are believed to stabilize an inactive receptor conformation. Thus, while an antagonist manifests its activity by virtue of inhibiting an agonist, an inverse agonist can additionally manifest its activity in the absence of an agonist by inhibiting the spontaneous conversion of an unliganded receptor to an active conformation.

[0038] The term “subject” refers to an animal, preferably a mammal, and most preferably a human, who is the object of treatment, observation or experiment. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans. The term “subject” also includes a domesticated animal, such as an animal useful for producing meat, preferably a domesticated fowl, bovine, ovine, caprine, or porcine animal.

[0039] The term “therapeutically effective amount” is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. This response may occur in a tissue, system, animal or human that is being sought by a researcher, veterinarian, farmer, medical doctor or other clinician, and includes alleviation of the symptoms of the disease being treated.

[0040] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject, wherein the subject is a domesticated animal useful for producing meat, milk, fish or eggs.

[0041] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating eating disorders requiring appetite stimulation.

[0042] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating a subject suffering from the symptoms of eating disorders requiring appetite stimulation.

[0043] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating wasting disorders.

[0044] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of promoting weight gain in a subject in need thereof.

[0045] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating gastro intestinal disorders.

[0046] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating cardiovascular disorders.

[0047] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating sleep disorders.

[0048] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating cancers.

[0049] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating hormone deficiencies.

[0050] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of diagnosing hormone deficiencies.

[0051] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating dwarfism, somatopause, catabolic states, and osteoporosis.

[0052] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating disorders of the pancreas, diabetes and control of glucose level.

[0053] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating anxiety and cognitive deficits.

[0054] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating disorders caused by inflammation or the symptoms of inflammation.

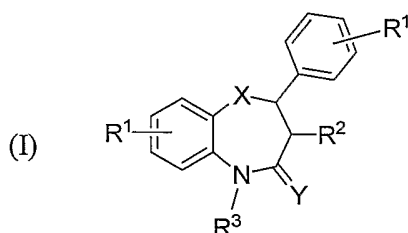
[0055] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating eating disorders requiring appetite reduction.

[0056] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I to a subject for the purpose of treating a subject suffering from the symptoms of eating disorders requiring appetite reduction.

[0057] In an embodiment, the methods of the present invention include administering a therapeutically effective amount of diltiazem, or diltiazem analogs of formula I, to a subject for the purpose of promoting weight loss in a subject in need thereof.

[0058] The term “treating” or “treatment” does not necessarily mean total cure. Any alleviation of any undesired signs or symptoms of the disease to any extent or the slowing down of the progress of the disease can be considered treatment. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well being or appearance. Treatment may also include lengthening the life of the patient, even if the symptoms are not alleviated, the disease conditions are not ameliorated, or the patient's overall feeling of well being is not improved.

[0059] In another aspect, disclosed herein is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen,

C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR₅, C(R₅)₂,

Wherein R₅ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

[0060] In certain embodiments, R₁ in the compound of Formula I is hydrogen, halogen, nitro, or OR₄, where R₄ is hydrogen or C₁-C₃ straight chained or branched alkyl. In other embodiments, R₁ is selected from the group consisting of hydrogen, hydroxy, nitro, chloro, bromo, methoxy, and ethoxy.

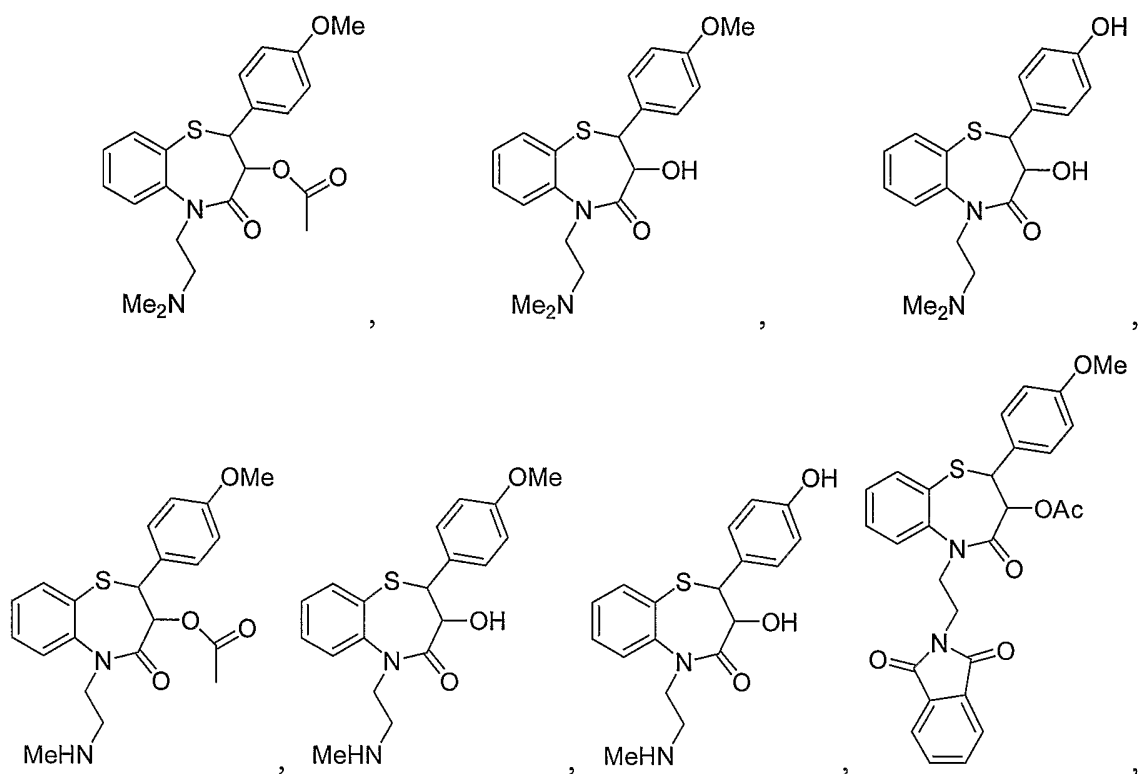
[0061] In some embodiments, R₂ in the compound of Formula I is selected from the group consisting of hydrogen, hydroxy, nitro, amino, halogen, -OR₈, -OCOR₈, and -N(R₈)₂, and wherein R₈ is hydrogen or C₁-C₄ straight chained or branched alkyl. In certain embodiments, R₂ is selected from the group consisting of hydrogen, hydroxy, and -OCOR₈, and wherein R₈ is C₁-C₄ straight chained or branched alkyl. In other embodiments, R₂ is selected from the group consisting of hydroxy, methoxy, and acetate.

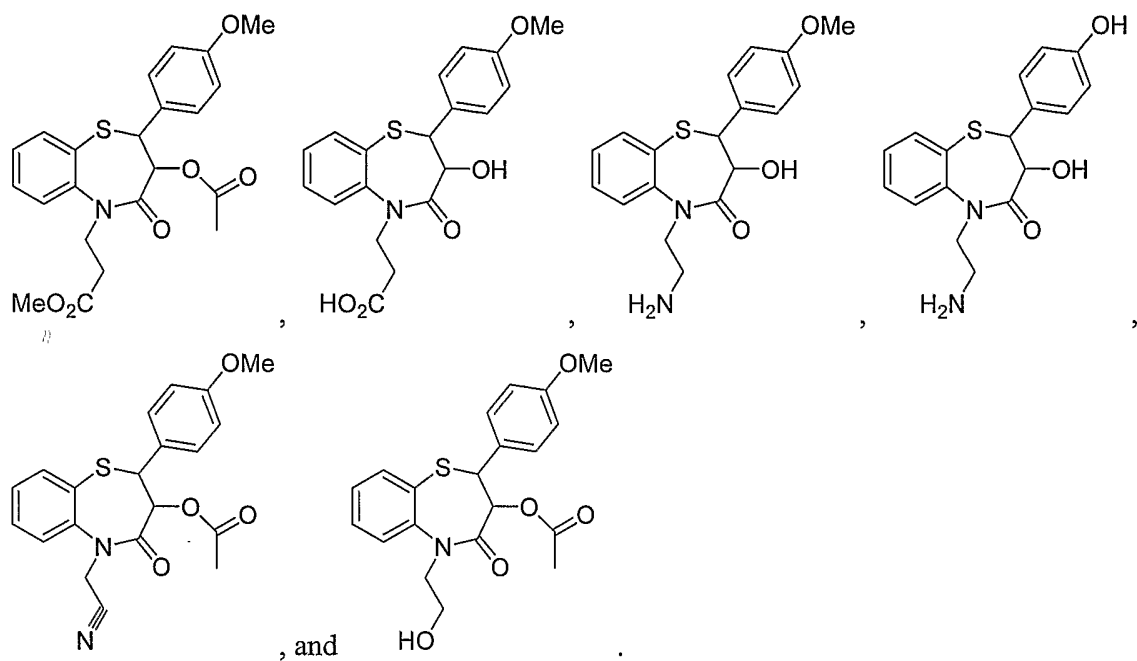
[0062] In certain embodiments, R₃ in the compound of Formula I is selected from the group consisting of hydrogen, (CH)_nR₉, where n can be 1-4 and wherein R₉ is hydrogen or -N(R₁₀)₂, heterocycle or heteroaryl optionally substituted, hydroxy, cyano, CO₂R₁₀, and wherein R₁₀ is selected from the group consisting of hydrogen, C₁-C₄ straight chained alkyl. In some embodiments, R₃ is selected from the group consisting of (CH)_nR₉, where n is 2 and R₉ is NH₂, NHMe, NMe₂, CO₂H, CO₂Me, OH. In other embodiments R₃ is selected from the group consisting of (CH)_nR₉, where n is 1 and R₉ is nitrile.

[0063] Embodiments include those in which X in the compound of Formula I is sulfur. In some embodiments, X is selected from the group consisting of CH₂, oxygen, sulfur, and -NR₁₁, and wherein R₁₁ is selected from the group of hydrogen, C₁-C₃ straight chained alkyl optionally substituted with an aryl.

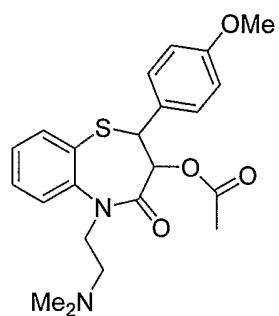
[0064] In further embodiments, Y in the compound of Formula I is selected from the group consisting of oxygen and sulfur. In certain embodiments, Y is oxygen.

[0065] In certain embodiments, the compound of Formula I is selected from the group consisting of:

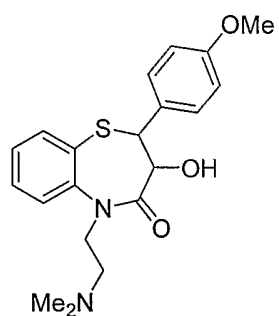




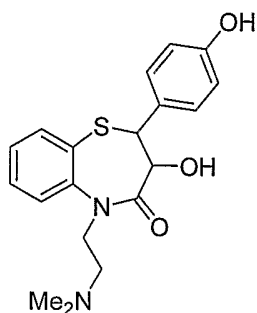
[0066] In certain embodiments, the compound of Formula I is not



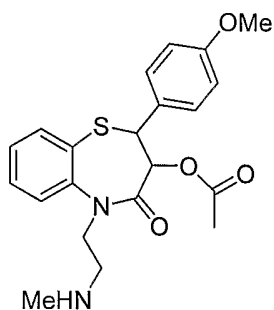
[0067] In certain embodiments, the compound of Formula I is not,



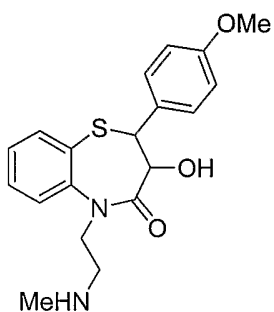
[0068] In certain embodiments, the compound of Formula I is not



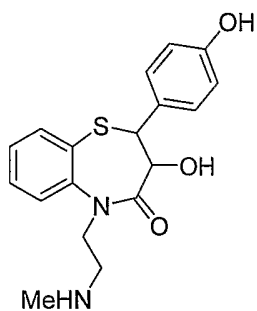
[0069] In certain embodiments, the compound of Formula I is not



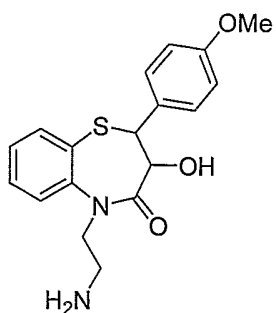
[0070] In certain embodiments, the compound of Formula I is not



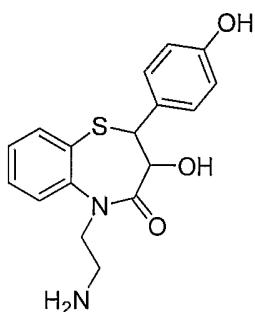
[0071] In certain embodiments, the compound of Formula I is not



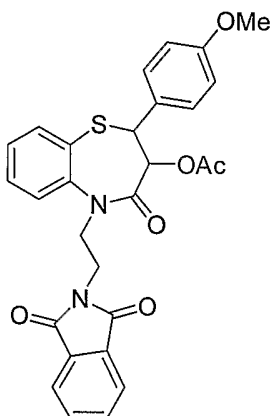
[0072] In certain embodiments, the compound of Formula I is not



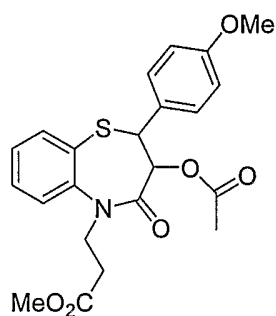
[0073] In certain embodiments, the compound of Formula I is not



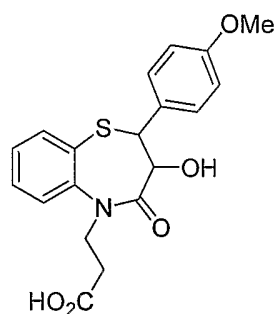
[0074] In certain embodiments, the compound of Formula I is not



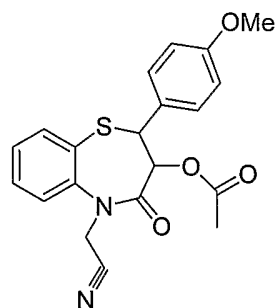
[0075] In certain embodiments, the compound of Formula I is not



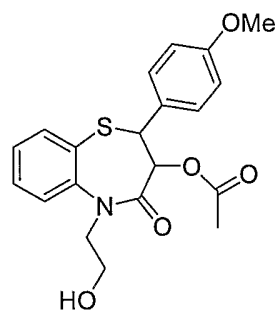
[0076] In certain embodiments, the compound of Formula I is not



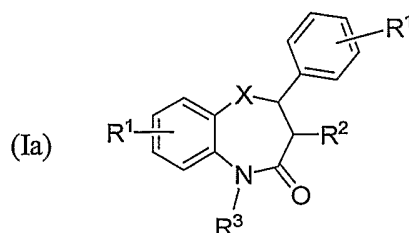
[0077] In certain embodiments, the compound of Formula I is not



[0078] In certain embodiments, the compound of Formula I is not



[0079] In another aspect, disclosed herein is a compound of Formula Ia



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, hydroxy, nitro, halogen, sulphonate, perhaloalkyl, $-OCH_3$, $-OCHF_2$, $-OCF_3$, $-OCH_2F$, $-OR_4$, $-N(R_4)_2$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, $-C(=O)R_4$, $-C(=O)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-OC(=O)R_4$, $-SR_4$, $-SOR_4$, $-SO_2R_4$, and $-SO_2N(R_4)_2$,

wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted and C_3 - C_7 cycloalkyl;

X is selected from the group consisting of oxygen, CH_2 and sulphur;

R_2 is selected from the group consisting of hydrogen, C_1 - C_4 straight chained or branched alkyl, hydroxy, perhaloalkyl, $-OR_5$, $-CN$, $-OC(=O)R_5$ and $-SR_5$,

wherein R_5 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl and heteroaryl optionally substituted;
and

R_3 is selected from the group consisting of hydrogen, and $-(CH)_nR_7$, wherein n is 1, 2, 3, or 4, and

R₇ is selected from the group consisting of -N(R₈)₂ and a heterocycle, wherein each R₈ is independently hydrogen or C₁-C₄ straight chained alkyl, or wherein both R₈ taken together with the nitrogen atom to which they are attached form a C₂-C₈ heterocycle.

[0080] In certain embodiments, R₁ in the compound of Formula I is hydrogen, halogen, nitro, or -OR₄, where R₄ is hydrogen or C₁-C₃ straight chained or branched alkyl. In other embodiments, R₁ is selected from the group consisting of hydrogen, hydroxy, chloro, bromo, -CF₃, methoxy, -OCF₃ and ethoxy.

[0081] In some embodiments, R₂ in the compound of Formula I is selected from the group consisting of hydrogen, hydroxy, -OR₅, and -OCOR₅, wherein R₅ is hydrogen or C₁-C₄ straight chained or branched alkyl. In certain embodiments, R₂ is selected from the group consisting of hydrogen, hydroxy and -OCOR₅, wherein R₅ is C₁-C₄ straight chained or branched alkyl. In other embodiments, R₂ is selected from the group consisting of hydroxy, methoxy and acetate.

[0082] In some embodiments, R₃ is selected from the group consisting of - (CH)_nR₇, wherein n is 1, 2, 3 or 4, and R₇ is -NH₂, -NHMe, -NMe₂, azetidine, pyrrolidine or piperidine.

[0083] Embodiments include those in which X in the compound of Formula I is sulfur.

[0084] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound disclosed herein with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound disclosed herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine,

tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0085] The term “ester” refers to a chemical moiety with formula $-(R)_n-COOR'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

[0086] An “amide” is a chemical moiety with formula $-(R)_n-C(O)NHR'$ or $-(R)_n-NHC(O)R'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of disclosed herein, thereby forming a prodrug.

[0087] Any amine, hydroxy, or carboxyl side chain on the compounds disclosed herein can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated by reference herein in its entirety.

[0088] Any ester, amide or any other carboxylic acid derivative on the compounds disclosed herein can be hydrolyzed. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, above.

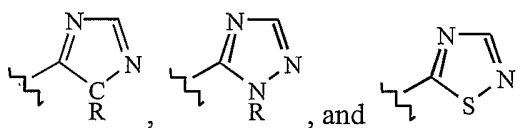
[0089] A “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound disclosed herein, which is administered as an ester (the “prodrug”) to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water solubility is beneficial. A further example of a prodrug might be a short

peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[0090] The term “aromatic” refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term “carbocyclic” refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. The term “heteroaromatic” or “heteroaryl” refers to an aromatic group which contains at least one heterocyclic ring.

[0091] Examples of aryl ring include, but are not limited to, benzene, and substituted benzene, such as toluene, aniline, xylene, and the like, naphthalene and substituted naphthalene, and azulene.

[0092] Examples of heteroaryl ring include, but are not limited to, furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine,

piperazine, triazine, , where R is as defined herein.

[0093] The term “heterocyclic” refers to saturated or unsaturated rings with from three to twelve units, contains at least one heteroatom selected from nitrogen, oxygen, sulfur, optionally condensed with another aromatic or non-aromatic ring.

[0094] Examples of heterocyclic rings are: Pyrrolidine, piperidine, dihydropiperidine, dihydropyridine, piperazine, morpholine, thiazine, indoline.

[0095] As used herein the term “cycloalkyl” refers to the univalent group derived from monocyclic hydrocarbons (with or without side chains) (E.g. cyclobutane) by removal of a hydrogen atom from the ring. The cycloalkyl moiety may be a “saturated cycloalkyl” group, which means that it does not contain any alkene or alkyne moieties. The cycloalkyl moiety may also be an “unsaturated cycloalkyl” moiety, which means that it contains at least

one alkene or alkyne moiety. The cyclalkyl moiety, whether saturated or unsaturated, may be branched.

[0096] Examples of cycloalkyl groups are, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl.

[0097] As used herein, the term “alkyl” refers to an aliphatic hydrocarbon group. The alkyl moiety may be a “saturated alkyl” group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an “unsaturated alkyl” moiety, which means that it contains at least one alkene or alkyne moiety. An “alkene” moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an “alkyne” moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0098] The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 5 carbon atoms. The alkyl group of the compounds disclosed herein may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[0099] The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and

the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted" that substituent may be substituted with one of the above substituents.

[0100] The term "alkylene" refers to an alkyl group, as defined here, which is a biradical and is connected to two other moieties. Thus, methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), proylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), isopropylene ($-\text{CH}_2-\text{CH}(\text{CH}_3)-$), and isobutylene ($-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$) are examples, without limitation, of an alkylene group.

[0101] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

[0102] An "O-carboxy" group refers to a $\text{RC}(=\text{O})\text{O}-$ group, where R is as defined herein.

[0103] A "C-carboxy" group refers to a $-\text{C}(=\text{O})\text{OR}$ groups where R is as defined herein.

[0104] An "acetyl" group refers to a $-\text{C}(=\text{O})\text{CH}_3$, group.

[0105] A "trihalomethanesulfonyl" group refers to a $\text{X}_3\text{CS}(=\text{O})_2-$ group where X is a halogen.

[0106] A "cyano" group refers to a $-\text{CN}$ group.

[0107] An "isocyanato" group refers to a $-\text{NCO}$ group.

[0108] A "thiocyanato" group refers to a $-\text{CNS}$ group.

[0109] An "isothiocyanato" group refers to a $-\text{NCS}$ group.

[0110] A "sulfinyl" group refers to a $-\text{S}(=\text{O})-\text{R}$ group, with R as defined herein.

[0111] A "S-sulfonamido" group refers to a $-\text{S}(=\text{O})_2\text{NR}$, group, with R as defined herein.

[0112] A "N-sulfonamido" group refers to a $\text{RS}(=\text{O})_2\text{NH}-$ group with R as defined herein.

[0113] A "trihalomethanesulfonamido" group refers to a $\text{X}_3\text{CS}(=\text{O})_2\text{NR}-$ group with X and R as defined herein.

[0114] An “O-carbamyl” group refers to a $-OC(=O)-NR$, group-with R as defined herein.

[0115] An “N-carbamyl” group refers to a $ROC(=O)NH-$ group, with R as defined herein.

[0116] An “O-thiocarbamyl” group refers to a $-OC(=S)-NR$, group with R as defined herein.

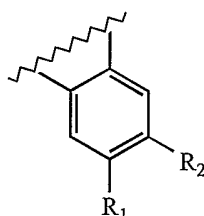
[0117] An “N-thiocarbamyl” group refers to an $ROC(=S)NH-$ group, with R as defined herein.

[0118] A “C-amido” group refers to a $-C(=O)-NR_2$ group with R as defined herein.

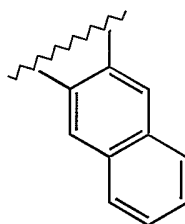
[0119] An “N-amido” group refers to a $RC(=O)NH-$ group, with R as defined herein.

[0120] The term “perhaloalkyl” refers to an alkyl group where one or more of the hydrogen atoms are replaced by halogen atoms.

[0121] When two substituents and the carbons to which they are attached form a ring, it is meant that the following structure:

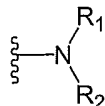


is representative of the following structure:

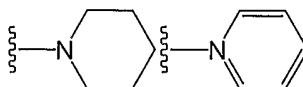


[0122] In the above example, R_1 and R_2 and the carbons to which they are attached form a six-membered aromatic ring. Those of skill in the art recognize that R_1 and R_2 can put together form a ring, whether aromatic or non-aromatic, of any size.

[0123] When two substituents and the nitrogen to which they are attached form a ring, such as a heteroaryl or heterocyclic ring; it is meant that the following structure:



is representative of, for example, the following structures:

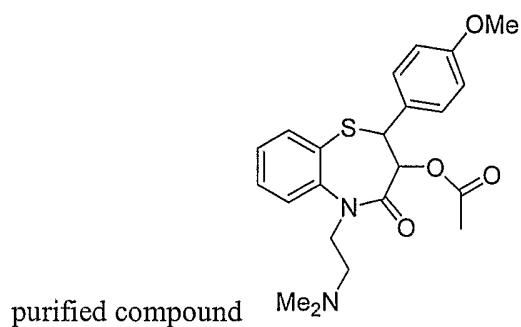


[0124] Unless otherwise indicated, when a substituent is deemed to be “optionally substituted,” it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heterocyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

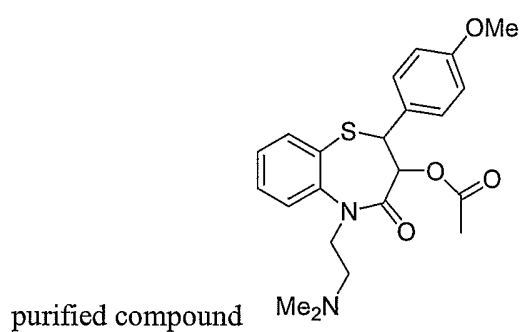
[0125] Certain of the compounds disclosed herein may exist as stereoisomers including optical isomers. The scope of the present disclosure includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

[0126] In certain embodiments, the present invention relates to an isolated or purified compound of Formula I, as defined herein.

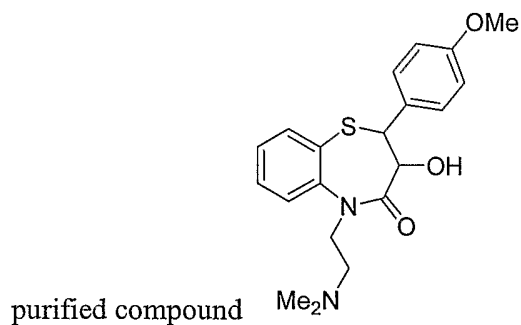
[0127] In certain embodiments, the present invention relates to isolated or



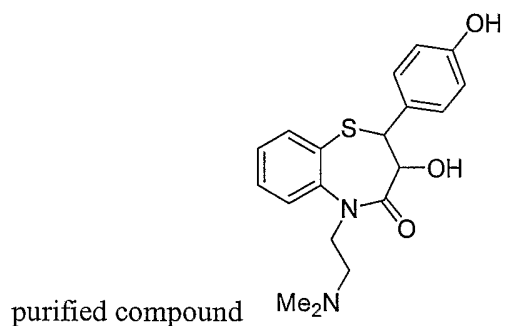
[0128] In certain embodiments, the present invention relates to isolated or



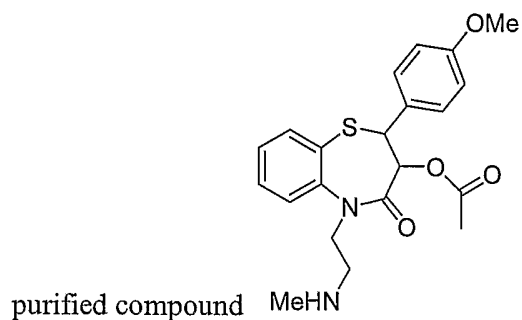
[0129] In certain embodiments, the present invention relates to isolated or



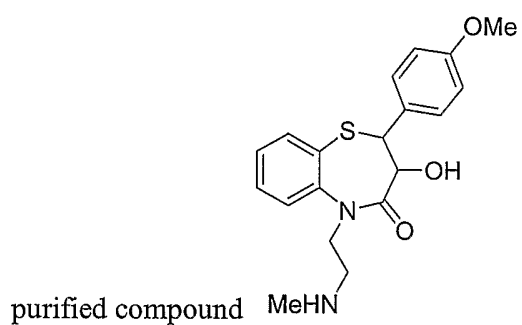
[0130] In certain embodiments, the present invention relates to isolated or



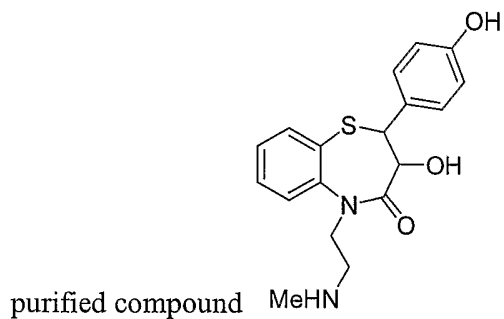
[0131] In certain embodiments, the present invention relates to isolated or



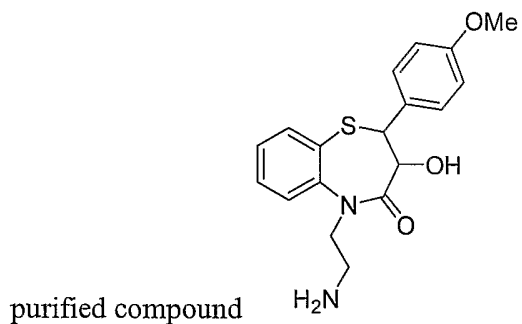
[0132] In certain embodiments, the present invention relates to isolated or



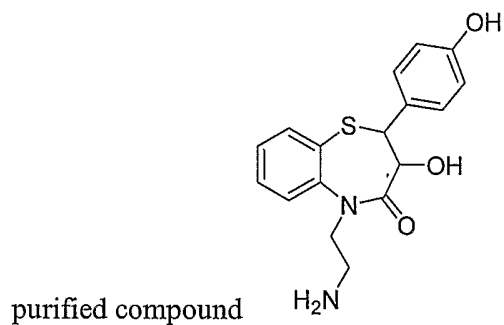
[0133] In certain embodiments, the present invention relates to isolated or



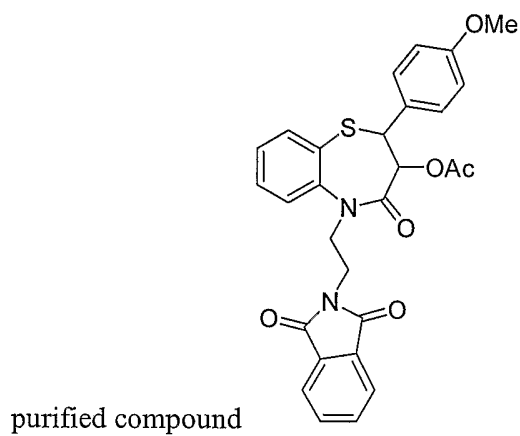
[0134] In certain embodiments, the present invention relates to isolated or



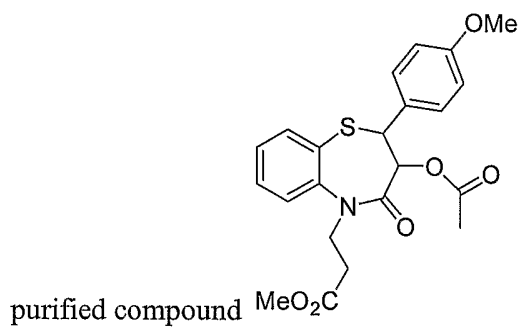
[0135] In certain embodiments, the present invention relates to isolated or



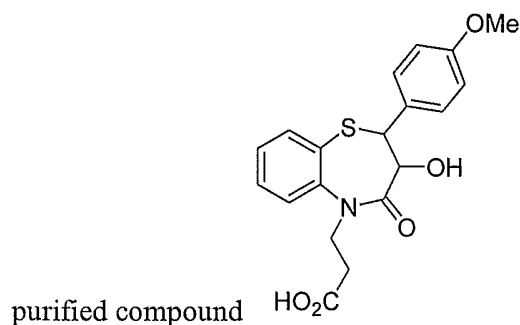
[0136] In certain embodiments, the present invention relates to isolated or



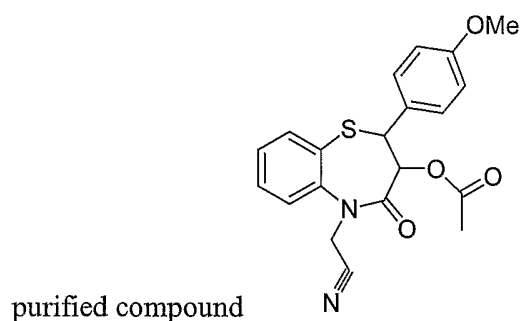
[0137] In certain embodiments, the present invention relates to isolated or



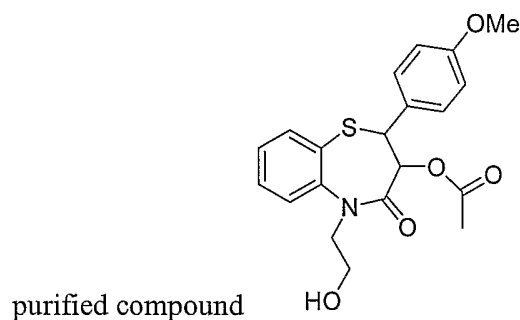
[0138] In certain embodiments, the present invention relates to isolated or



[0139] In certain embodiments, the present invention relates to isolated or



[0140] In certain embodiments, the present invention relates to isolated or



[0141] By “purified” it is meant that the particular compound exists, either in solid form or in solution, in a form that is greater than 50% pure. By “greater than 50% pure” it is meant that the particular compound constitutes greater than 50% of the compounds having a similar structure, i.e., the core structure of the compound of Formula I, in the composition. In some embodiments, the purified compound is in a form that is greater than 60% pure. In some embodiments, the purified compound is in a form that is greater than 70% pure. In some embodiments, the purified compound is in a form that is greater than 80% pure. In some embodiments, the purified compound is in a form that is greater than 90% pure. In some embodiments, the purified compound is in a form that is greater than

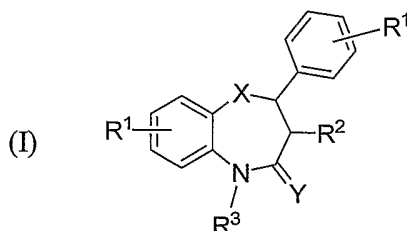
95% pure. In some embodiments, the purified compound is in a form that is greater than 97% pure. In some embodiments, the purified compound is in a form that is greater than 99% pure.

[0142] By “isolated” it is meant that the particular compound exists in a form free from solvents or other organic or inorganic materials. In some embodiments, the isolated compound is greater than 50% isolated, i.e., the particular compound constitutes greater than 50% of the composition by weight. In some embodiments, the purified compound is in a form that is greater than 60% isolated. In some embodiments, the purified compound is in a form that is greater than 70% isolated. In some embodiments, the purified compound is in a form that is greater than 80% isolated. In some embodiments, the purified compound is in a form that is greater than 90% isolated. In some embodiments, the purified compound is in a form that is greater than 95% isolated. In some embodiments, the purified compound is in a form that is greater than 97% isolated. In some embodiments, the purified compound is in a form that is greater than 99% isolated.

[0143] In some embodiments, the compound of Formula I is an agonist of the ghrelin receptor. In other embodiments, the compound of Formula I is an antagonist of the ghrelin receptor. In yet other embodiments, the compound of Formula I is an inverse agonist of the ghrelin receptor. Those of skill in the art can readily determine whether a compound of Formula I is an agonist, antagonist, or inverse agonist of the ghrelin receptor by following the RSAT procedure set forth in Example 1, below.

FORMULATION/PREPARATION OF DILTIAZEM

[0144] In another aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR_5 , $C(R_5)_2$,

Wherein R_5 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R_5 and the X may form C_3 - C_7 cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R_2 is selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_6$, $-N(R_6)_2$, $-CN$, $-C(=Z)R_6$, $-C(=Z)OR_6$, $-C(=Z)N(R_6)_2$, $-N(R_6)-C(=Z)R_6$, $-N(R_6)-C(=Z)N(R_6)_2$, $-OC(=Z)R_6$, and $-SR_6$, $-SOR_6$, $-SO_2R_6$,

wherein Z is oxygen or sulfur; and wherein each R_6 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

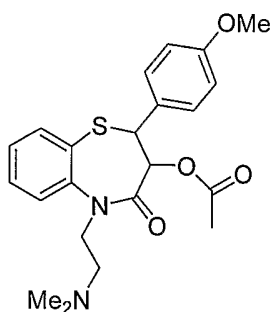
R_3 is selected from the group consisting of C_1 - C_4 straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, $-C(=Z)R_7$, $-C(=Z)OR_7$, and $-C(=Z)N(R_7)_2$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulphur,

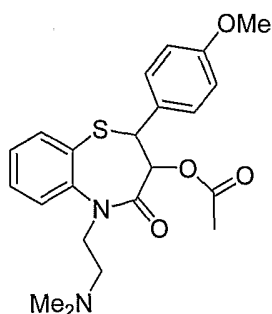
and a pharmaceutically acceptable diluent, excipient, or carrier.

[0145] In certain embodiments, the compound of Formula I in the above



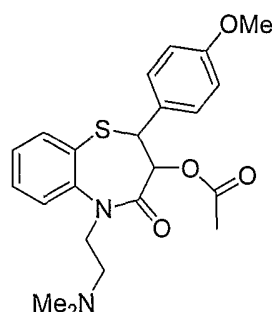
pharmaceutical composition is not

[0146] In certain embodiments, the compound of Formula I in the above



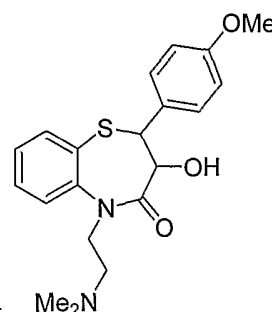
pharmaceutical composition is not

[0147] In certain embodiments, the compound of Formula I in the above



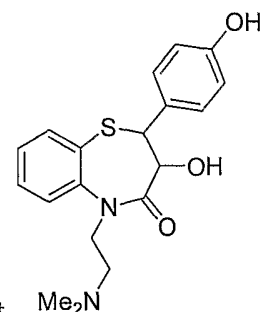
pharmaceutical composition is not

[0148] In certain embodiments, the compound of Formula I in the above



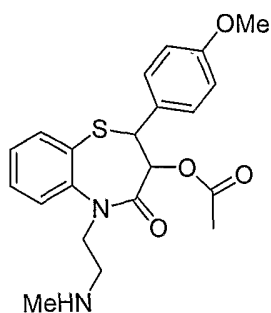
pharmaceutical composition is not

[0149] In certain embodiments, the compound of Formula I in the above



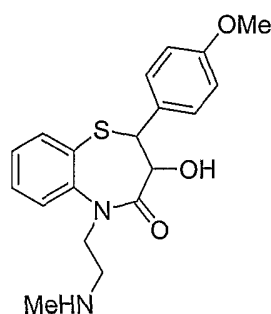
pharmaceutical composition is not

[0150] In certain embodiments, the compound of Formula I in the above



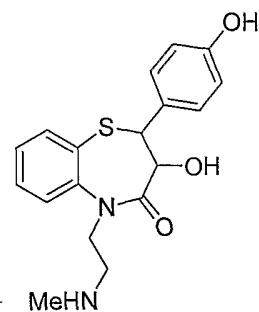
pharmaceutical composition is not MeHN .

[0151] In certain embodiments, the compound of Formula I in the above



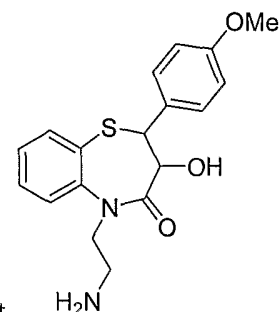
pharmaceutical composition is not MeHN .

[0152] In certain embodiments, the compound of Formula I in the above



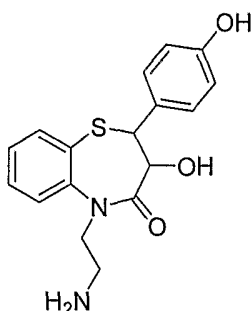
pharmaceutical composition is not MeHN .

[0153] In certain embodiments, the compound of Formula I in the above



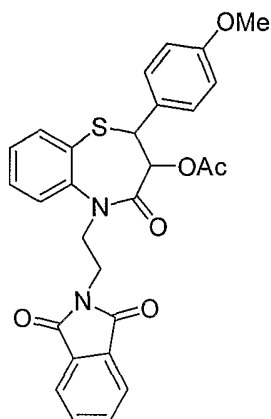
pharmaceutical composition is not H₂N .

[0154] In certain embodiments, the compound of Formula I in the above



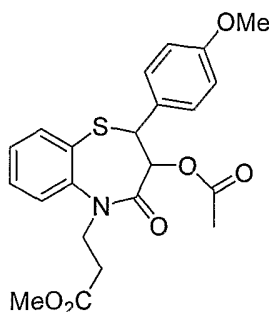
pharmaceutical composition is not

[0155] In certain embodiments, the compound of Formula I in the above



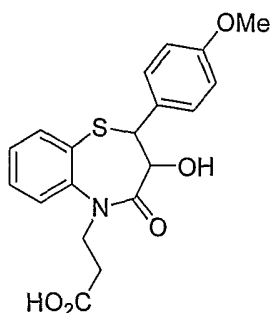
pharmaceutical composition is not

[0156] In certain embodiments, the compound of Formula I in the above



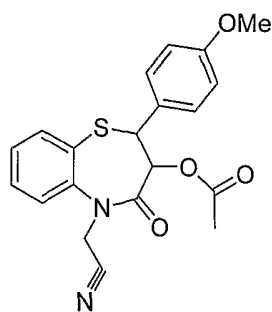
pharmaceutical composition is not

[0157] In certain embodiments, the compound of Formula I in the above



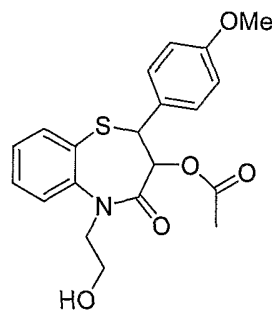
pharmaceutical composition is not

[0158] In certain embodiments, the compound of Formula I in the above



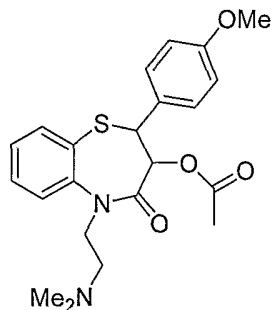
pharmaceutical composition is not

[0159] In certain embodiments, the compound of Formula I in the above



pharmaceutical composition is not

[0160] In another aspect, the present invention relates to a pharmaceutical

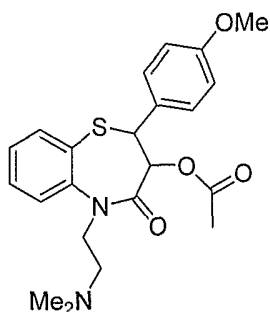


composition comprising

, and a pharmaceutically acceptable diluent,

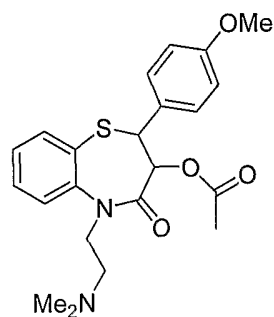
excipient, or carrier.

[0161] In another aspect, the present invention relates to a pharmaceutical



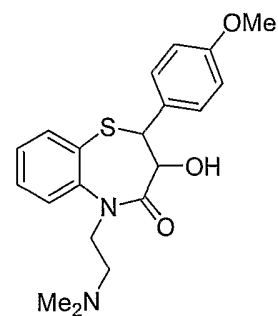
composition comprising , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0162] In another aspect, the present invention relates to a pharmaceutical



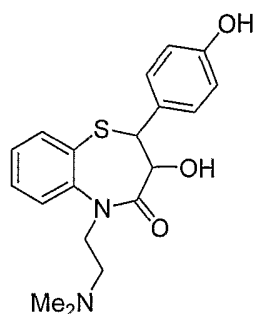
composition comprising , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0163] In another aspect, the present invention relates to a pharmaceutical



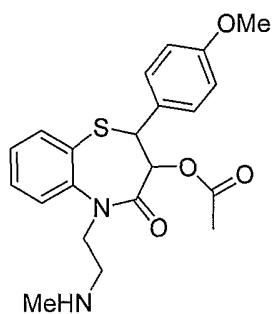
composition comprising , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0164] In another aspect, the present invention relates to a pharmaceutical



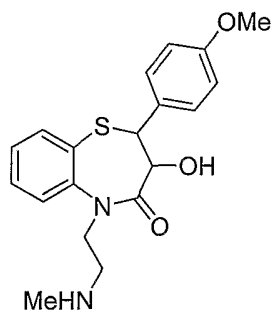
composition comprising Me2N, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0165] In another aspect, the present invention relates to a pharmaceutical



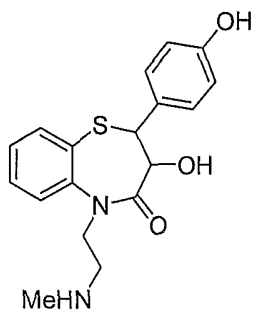
composition comprising MeHN, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0166] In another aspect, the present invention relates to a pharmaceutical



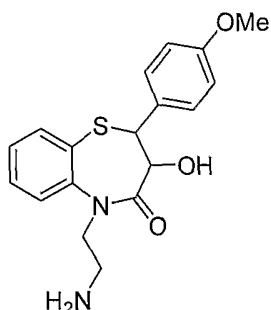
composition comprising MeHN, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0167] In another aspect, the present invention relates to a pharmaceutical



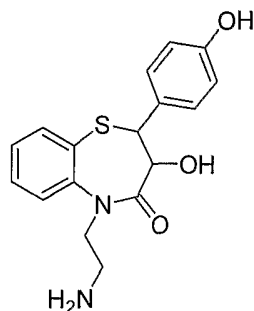
composition comprising MeHN, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0168] In another aspect, the present invention relates to a pharmaceutical



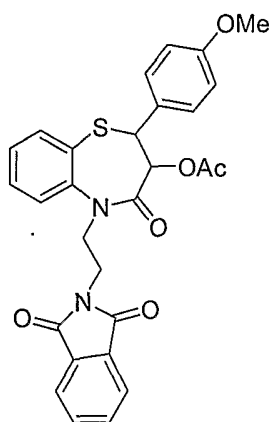
composition comprising H₂N, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0169] In another aspect, the present invention relates to a pharmaceutical



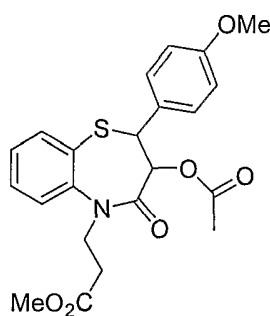
composition comprising H₂N, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0170] In another aspect, the present invention relates to a pharmaceutical



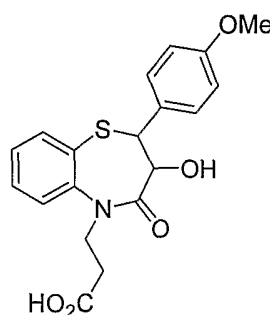
composition comprising , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0171] In another aspect, the present invention relates to a pharmaceutical



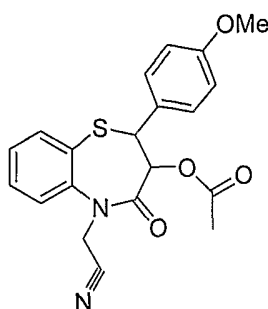
composition comprising MeO₂C , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0172] In another aspect, the present invention relates to a pharmaceutical



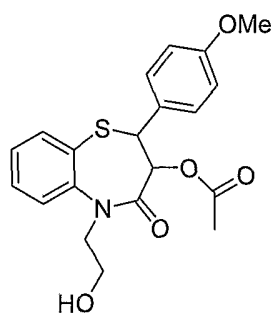
composition comprising HO₂C , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0173] In another aspect, the present invention relates to a pharmaceutical



composition comprising , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0174] In another aspect, the present invention relates to a pharmaceutical



composition comprising HO , and a pharmaceutically acceptable diluent, excipient, or carrier.

[0175] In certain embodiments, the above pharmaceutical compositions are used for the treatment of a ghrelin receptor related disease or disorder. In some of these embodiments the disease or disorder is selected from the group consisting of: an eating disorder, a wasting disorder, promotion of weight gain, a gastrointestinal disorder, a cardiovascular disorder, a sleep disorder, cancer, hormone deficiencies, dwarfism, somatopause, catabolic states, osteoporosis, disorders of the pancreas, diabetes, control of glucose levels, anxiety disorders, memory loss, memory impairment, a cognitive deficit, a neurodegenerative disorder and an inflammatory disorder.

[0176] In certain embodiments, the eating disorder is selected from the group consisting of anorexia nervosa, bulimia, cachexia and cancer cachexia.

[0177] In certain embodiments, the wasting disorder is selected from the group consisting of wasting, HIV induced wasting, AIDS related cachexia, wasting associated with surgical stress, cachexia of critical illness, wasting associated with sepsis, wasting associated with glucocorticoid administration, wasting associated with cancer and other catabolic states.

[0178] In certain embodiments, the promotion of weight gain can include reversing catabolic states.

[0179] In certain embodiments, the gastrointestinal disorder is selected from the group consisting of reduced gastric and intestinal motility, post-operative gastric ileus, delayed gastric emptying, delayed gastric emptying due to diabetes, delayed gastric emptying post-operatively, short bowel syndrome and a gastric ulcer.

[0180] In certain embodiments, the cardiovascular disorder is selected from the group consisting of angina, cardiac ischemia, cardiac failure, hypertension, atherosclerosis, and hypotension.

[0181] In certain embodiments, the sleep disorder is selected from the group consisting of insomnia, narcolepsy, catalepsy, somnolence, daytime somnolence, improving sleep architecture and facilitating induction of sleep.

[0182] In certain embodiments, treatment of cancer includes controlling unwanted cellular proliferation associated with cancer.

[0183] In certain embodiments, the hormone deficiencies are selected from the group consisting of deficiencies in producing growth hormone, ACTH, cortisol, insulin-like growth factor 1 (IGF-1), and prolactin.

[0184] In certain embodiments, the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Amyotrophic Lateral Sclerosis (ALS) and multiple sclerosis.

[0185] In certain embodiments, the inflammatory disorder is selected from the group consisting of rheumatoid arthritis and atherosclerosis.

[0186] In certain embodiments, the above pharmaceutical compositions are used for the promotion of weight gain in a subject in need thereof.

[0187] In certain embodiments, the above pharmaceutical compositions are used for controlling the appetite of a subject in need thereof.

[0188] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found

in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0189] Suitable routes of administration may, for example, include oral, rectal, topical, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0190] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

[0191] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0192] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0193] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0194] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the

art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0195] For topical administration, the compounds may be formulated for administration to the epidermis as ointments, gels, creams, pastes, salves, gels, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

[0196] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0197] Pharmaceutical preparations which can be used orally, including sublingually, which include include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In

soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0198] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0199] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0200] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0201] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0202] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0203] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0204] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0205] A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0206] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those

skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0207] Many of the compounds used in the pharmaceutical combinations of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

[0208] Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0209] The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. Note that for almost all of the specific compounds mentioned in the present disclosure, human dosages for treatment of at least some condition have been established. Thus, in most instances, the present invention will use those same dosages, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived

from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0210] Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 6000 mg of each ingredient, preferably between 1 mg and 5000 mg, e.g. 25 to 5000 mg or an intravenous, subcutaneous, or intramuscular dose of each ingredient between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg of each ingredient of the pharmaceutical compositions of the present invention or a pharmaceutically acceptable salt thereof calculated as the free base, the composition being administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of each ingredient up to 400 mg per day. Thus, the total daily dosage by oral administration of each ingredient will typically be in the range 1 to 2500 mg and the total daily dosage by parenteral administration will typically be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0211] In one embodiment, the dose of the pharmaceutical composition comprising praziquantel or a pharmaceutically acceptable salt, prodrug, ester or amide thereof, is from about 10 to about 50 mg per day.

[0212] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0213] Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0214] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0215] The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

[0216] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0217] The compositions described herein may also be used in the preparation of a medicament for treatment of any of the disorders described above.

[0218] Diltiazem (CAS registry number 33286-22-5) can be prepared in a number of formulations as described (5, see Table 1). Diltiazem can be chemically synthesized as previously described (6).

Table 1. Formulations of Diltiazem (taken from Ref. 5).

I. PREPARATIONS**Diltiazem Hydrochloride****Oral**

Capsules, extended- release	60mg*	Cardizem® SR (12 hours; with povidone), Biovail
	90mg*	Cardizem® SR (12 hours; with povidone), Biovail
	120mg*	Cardizem® CD (24 hours), Biovail Cardizem® SR (12 hours; with povidone), Biovail Cartia XT® , Andrx Tiazac® (24 hours; with povidone), Forest
	180mg*	Cardizem® CD (24 hours), Biovail Cartia XT® , Andrx Tiazac® (24 hours; with povidone), Forest
	240mg*	Cardizem® CD (24 hours), Biovail Cartia XT® , Andrx Tiazac® (24 hours; with povidone), Forest
	300mg*	Cardizem® CD (24 hours), Biovail Cartia XT® , Andrx Tiazac® (24 hours; with povidone), Forest
	360mg	Cardizem® CD (24 hours), Biovail Tiazac® (24 hours; with povidone), Forest
	420mg	Tiazac® (24 hours; with povidone), Forest
Capsules, extended- release (containing multiple 60-mg tablets)	120mg	Dilacor XR® (24 hours), Watson Diltia XT® (24 hours), Andrx
	180mg	Dilacor XR® (24 hours), Watson Diltia XT® (24 hours), Andrx
	240mg	Dilacor XR® (24 hours), Watson Diltia XT® (24 hours), Andrx

Tablets	30mg*	Cardizem® (with methylparaben), Biovail
	60mg*	Cardizem® (with methylparaben; scored), Biovail
	90mg*	Cardizem® (with methylparaben; scored), Biovail
	120mg*	Cardizem® (with methylparaben; scored), Biovail

Parenteral

For Injection	25mg	Cardizem® Lyo-Ject® (with mannitol and diluent containing benzyl alcohol in dual-chambered syringe), Biovail
For injection, for IV infusion only	100mg	<u>Cardizem® Monovial®, Biovail</u>
Injection	5mg/mL (25 and 50mg)*	Cardizem® (with sorbitol), Biovail

*available by nonproprietary name.

[0219] Diltiazem can be formulated in pharmaceutical compositions comprising diltiazem together with a pharmaceutically acceptable diluant or excipient. Such compositions can be formulated in an appropriate manner and in accordance with accepted practices such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton PA, 1990. Diltiazem may be formulated in any of the formulations described in Table 1 or reference 5.

[0220] Advantageously, diltiazem, or diltiazem analogs of formula I can be administered in a single daily dose, or the total daily dosage can be administered in divided doses two, three or four times daily. Furthermore, compound for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, or via topical use of ocular formulations, or using those forms of

transdermal skin patches well known to persons skilled in the art or in any of the formulations described in Table 1 or reference 5.

[0221] The dosage regimen of diltiazem, or diltiazem analogs of formula I are selected in accordance with a variety of factors. These include 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 employed. A physician of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the disease or disorder that is being treated.

[0222] The daily dosage of the products can be varied over a wide range from 0.01 to 1000 mg per adult human per day. An effective amount of the drug is ordinarily supplied at a dosage level of about 0.0001 mg/kg to about 25 mg/kg body weight per day. Preferably, the range is from about 0.001 to 10 mg/kg of body weight per day, and especially from about 0.001 mg/kg to 1 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

[0223] Diltiazem, or diltiazem analogs of formula I can be used alone at appropriate dosages defined by routine testing in order to obtain optimal pharmacological effect, while minimizing any potential toxic or otherwise unwanted effects. In addition, it is believed that diltiazem, or diltiazem analogs of formula I can be used, as adjunctive therapy with known drugs to reduce the dosage required of these traditional drugs, and thereby reduce their side effects.

[0224] Defining the functional pharmacological activity of diltiazem, or diltiazem analogs of formula I at a given receptor can be achieved by a variety of methodologies. A currently favored assay is the Receptor Selection and Amplification Technology (R-SAT) assay disclosed in US 5,707,798, the content of which is hereby incorporated by reference in its entirety.

[0225] Defining the functional pharmacological activity of diltiazem, or diltiazem analogs of formula I at a given receptor can be achieved by a variety of methodologies. Another currently favored assay is the Phosphatidyl Inositol (PI) Hydrolysis assay (7).

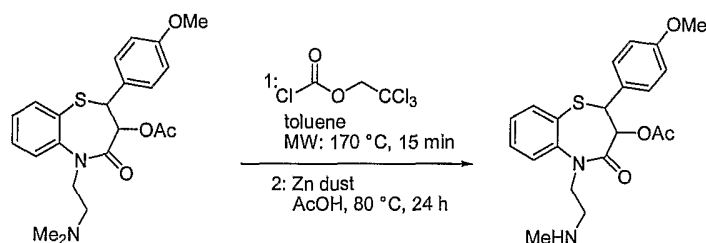
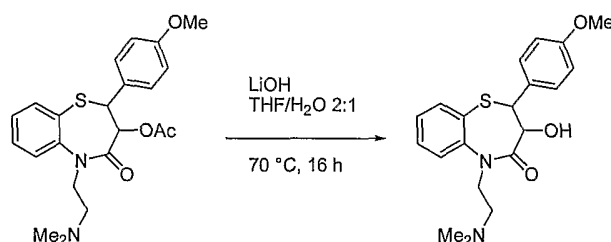
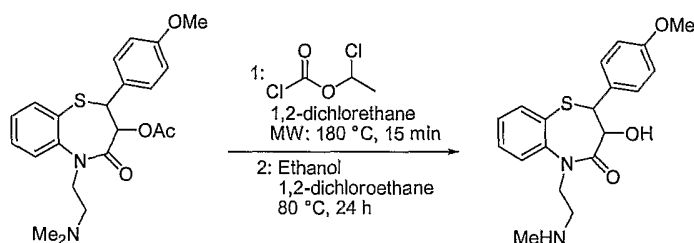
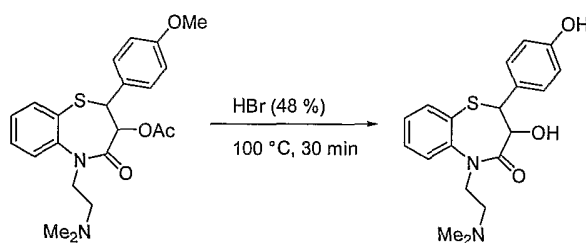
[0226] Defining the activity of diltiazem, or diltiazem analogs of formula I to activate Ghrelin receptors *in vivo* can be achieved by a variety of methodologies. A currently favored assay is the growth hormone release assay (8).

[0227] Defining the activity of diltiazem, or diltiazem analogs of formula I to reduce inflammation *in vivo* can be achieved by a variety of methodologies. A currently favored assay is the paw edema model. Paw edema is induced by injecting 50 μ L of 1% carrageenan in saline into the subplantar region of the left hind paw. The controls are given the same volume of sterile saline as in test groups. Carrageenan-induced rat paw edema or extent of the edema thickness (foot-pad) is measured in conscious rats 3-4 h after injections. For testing anti-inflammatory activity, vehicle and test drugs are first given i.p. 30 min before carrageenan injection.

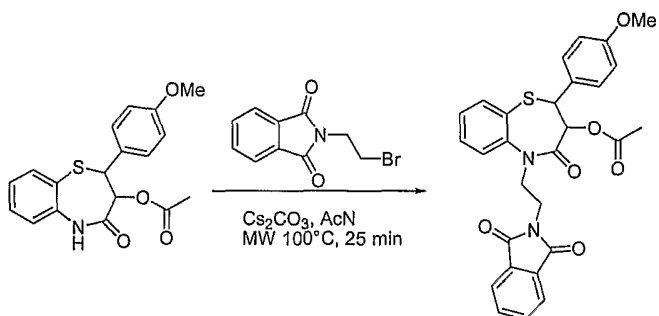
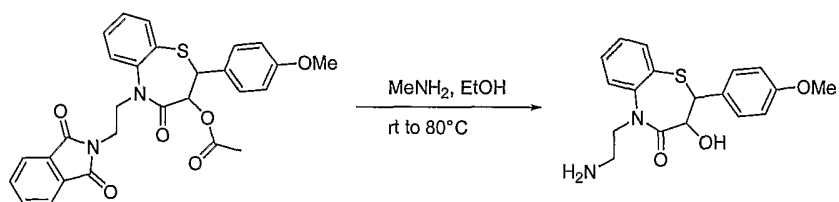
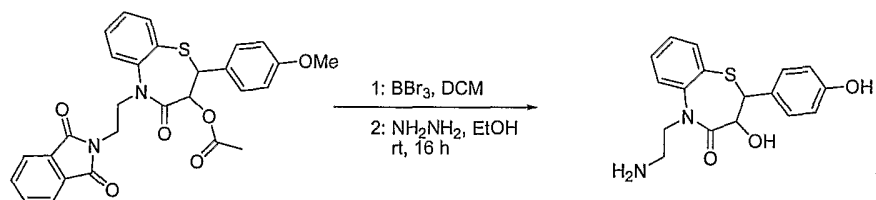
[0228] Defining the activity of diltiazem, or diltiazem analogs of formula I to stimulate feeding *in vivo* can be achieved by a variety of methodologies. A currently favored assay is measuring spontaneous feeding in freely feeding rats. Male Harlan Sprague-Dawley rats (~150 g) are provided with free access to food/water (1800-0600 12 h dark/light cycle). All rats are injected (i.p.) ~11 am with vehicle (5% DMSO/95% saline, 0.3 mL/rat). Four hours later, rats are given 2nd ip injection with test drugs. Immediately after 2nd injection the rats are returned to individual cages with a pre-weighed amount of regular chow (~70 g/cage). Food intake is measured at 1 h post-2nd injection.

SYNTHESIS

[0229] General synthetic routes to the compounds of this invention are shown in Schemes 1-8. The routes shown are illustrative only and are not intended, nor are they to be construed, to limit the scope of this invention in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed synthesis and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of this invention.

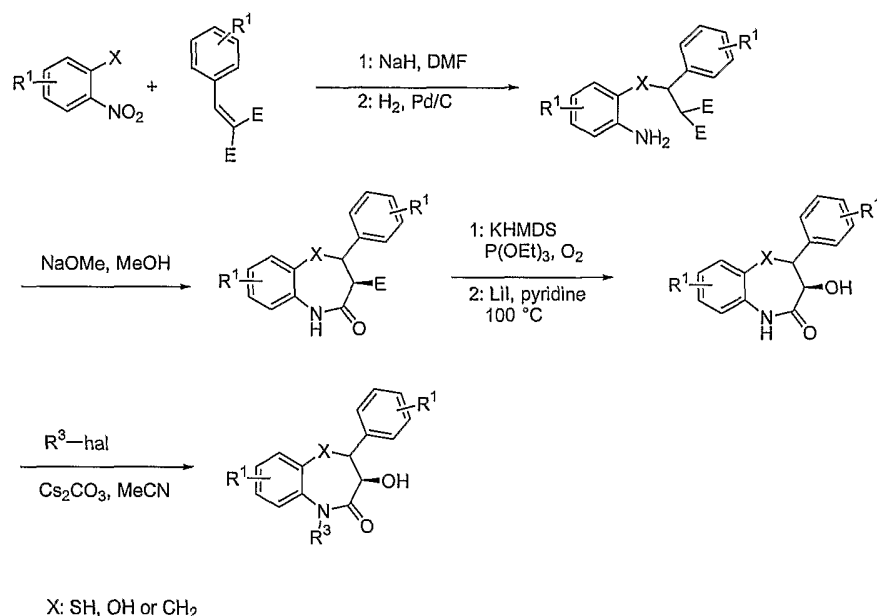
I. SYNTHESIS OF DILTIAZEM METABOLITES**Scheme 1¹³:****Scheme 2:****Scheme 3¹⁴:****Scheme 4:**

Scheme 5:

Scheme 6¹⁵:Scheme 7¹⁶:

II. SYNTHESIS OF THE GENERIC STRUCTURE

Scheme 8:



[0230] The present invention is further disclosed in the following examples, which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

Example 1: Receptor Selection and Amplification Technology (R-SAT)

[0231] The functional receptor assay, Receptor Selection and Amplification Technology (R-SAT), was used (essentially as disclosed in US 5,707,798) to investigate the functional pharmacological properties of known drugs, including many of their metabolites. These experiments have provided a molecular profile, or fingerprint, for each of these agents. Of all of the agents tested, only one, diltiazem, displayed potent ghrelin receptor agonist activity as disclosed in **Figure 1**. Diltiazem is a partial agonist with 69% efficacy relative to the ghrelin receptor reference agonist GHRP-6 (Tables 2 & 3). To confirm the observation that diltiazem displays ghrelin receptor agonist activity, a PI hydrolysis assay was performed, the results of which are disclosed in **Figure 2**. Diltiazem is a ghrelin receptor agonist in this system with substantial efficacy (93% relative efficacy to GHRP-6) (Table 3). Thus, two

distinct functional assays confirm that diltiazem possesses previously unappreciated potent and fully efficacious agonist activity at human ghrelin receptors.

[0232] Data presented in **Figure 1** are derived from R-SAT assays as previously previously described (7). The concentration response relationships of GHRP-6, diltiazem, and analogs of Formula I to activate human Ghrelin receptors are shown. Data are plotted as response in absorbance units. Potency is reported as $-pEC_{50}$ values, and efficacy is reported as that relative to the reference agonist GHRP-6 (**Table 2** and **Table 3**).

[0233] Data presented in **Figure 2** are derived from PI assays as described in (7). The concentration response relationships of GHRP-6, diltiazem, and analogs of Formula I to activate human Ghrelin receptors are shown. Data are plotted as a radioactivity measured in counts per minute versus drug concentration. Potency is reported as $-pEC_{50}$ values, and efficacy is reported as that relative to the reference agonist GHRP-6 (**Table 3**).

[0234] To confirm aspects of this molecular profile *in vivo*, diltiazem was administered subcutaneously to rats, and the ghrelin receptor mediated release of growth hormone was determined, and this is disclosed in **Figure 3**. Rats were treated i.p. with vehicle, diltiazem (1, 3, or 10 mg/kg) or **III** (1, 3, or 10 mg/kg). At 15 min post-dosing, rats were sacrificed, blood samples taken, and analyzed for growth hormone levels using the rat EIA GH kit from Cayman (cat # 589601-1) according to the manufacturers instructions. Robust growth hormone release was observed for both diltiazem and **III** at doses of 3 and 10 mg/kg. This confirms that diltiazem and analogs of Formula I function as a ghrelin receptors agonist *in-vivo*.

Table 2: Agonist activity of diltiazem and diltiazem analogs of formula I in R-SAT assays: Dissociation of Ghrelin receptor activity from Ca^{2+} channel blocking activity

7

Ligand	GHSR1		Ca^{2+} channel* pIC50
	pEC50	Eff(%)	
Diltiazem	6.4	69	6.9
I	6.5	102	6.5
II	6.8	88	6.7
III	6.7	108	6.0

*taken from ref 9

[0235] Because diltiazem possesses potent Ca^{2+} channel blocking activity, analogs of diltiazem with lower potency at Ca^{2+} channels were tested for agonist activity in RSAT. As shown in **Table 2**, several analogs with lower affinity for Ca^{2+} channels had increased potency and efficacy compared with diltiazem at the ghrelin receptor.

[0236] To confirm the enhanced activity of diltiazem analogs of formula I, diltiazem and diltiazem analogs of formula I were tested in Ca^{2+} mobilization assays. HEK293T cells transfected with human ghrelin receptors at a density $1\text{--}3 \times 10^6$ cells/ml are washed with phosphate-buffered saline, loaded with 2 μM Fura-2 and analyzed with respect to the rise in intracellular calcium in the presence or absence of varying concentrations of compound. The response is compared to the maximum response elicited by the application of the standard reference ligands GHRP-6. Intracellular free calcium concentrations are calculated using the formula:

$$[\text{Ca}^{2+}]_i = \frac{K_d(F - F_{\min})}{F_{\max} - F}$$

[0237] where K_d for Fura-2 is 224 nM, $F_{\max}$ is the fluorescence in the presence of 0.04% Triton-X100 and $F_{\min}$ is the fluorescence obtained. As shown in **Figure 4** and **Table 3**, the enhanced potency and efficacy of several diltiazem analogues that was observed in RSAT was confirmed in Ca^{2+} mobilization assays.

Table 3. Agonist activity of diltiazem and diltiazem analogs of formula I across in vitro functional assays:

RSAT		
Ligand	pEC50	Eff(%)
Diltiazem	6.4 +/-0.5	69 +/-28
I	6.5 +/-0.3	102 +/-14
II	6.8 +/-0.4	88 +/-14
III	6.7 +/-0.4	108 +/-19
GHRP-6	8.3 +/-0.7	100 +/-9
Ca2+ mobilization		
Diltiazem	5.1 +/-0.2	36 +/-1
I	5.4 +/-0.1	95 +/-36
II	6.2 +/-0.1	72 +/-29
III	6.9 +/-0.6	88 +/-24
GHRP-6	8.2 +/-0.3	100 +/-0
PI hydrolysis		
Diltiazem	5.9 +/-0.1	92 +/-19
I	6.0 +/-0.3	85 +/-22
II	6.9 +/-0.2	71 +/-6
III	6.8 +/-0.2	77 +/-6
GHRP-6	8.8 +/-0.5	100 +/-0

[0238] Because ghrelin has been reported to possess anti-inflammatory properties (10-12), diltiazem and analogs of Formula I were tested in the rat paw edema assay, a measure of inflammation. Paw edema was induced by injecting 50ul of 1% carrageenan in saline into the subplantar region of the left hind paw of Sprague-Dawley rats. The controls were given the same volume of sterile saline as in test groups. For testing anti-inflammatory activity, vehicle and test drugs were first given i.p. 30 min before carrageenan injection. Carrageenan-induced rat paw edema or extent of the edema thickness (foot-pad) was measured in conscious rats 3-4h after injections. As shown in **Figure 5**, diltiazem and analogs of Formula I administered systemically significantly reduced carrageenan-induced swelling. Thus diltiazem and analogs of Formula I possess anti-inflammatory properties.

[0239] Because ghrelin has been reported to stimulate appetite and food intake (1-4), diltiazem and analogs of Formula I were tested for the ability to stimulate feeding in freely feeding rats. Male Harlan Sprague-Dawley rats (~150 g) were provided with free access to food/water (1800-0600 12 h dark/light cycle). All rats are injected (i.p.) ~11 am with vehicle (5% DMSO/95% saline, 0.3 mL/rat). Four hours later, rats were given 2nd ip inj with test

drugs. Immediately after 2nd injection the rats were returned to individual cages with a pre-weighed amount of regular chow (~70 g/cage). Food intake was measured at 1 h post-2nd injection. As shown in **Figure 6**, diltiazem and analogs of Formula I administered systemically significantly stimulated food intake. Thus diltiazem and analogs of Formula I possess appetite stimulating properties.

Example 2: Synthetic Chemistry

General Analytical LC-MS procedure

Procedure 1 (AP1):

[0240] The analysis was performed on a combined prep/analytical Waters/Micromass system consisting of a ZMD single quadropole mass spectrometer equipped with electro-spray ionization interface. The HPLC system consisted of a Waters 600 gradient pump with on-line degassing, a 2700 sample manager and a 996 PDA detector.

[0241] Separation was performed on an X-Terra MS C18, 5 μ m 4.6x50mm column. Buffer A: 10 mM ammoniumacetate in water, buffer B: 10 mM ammoniumacetate in acetonitrile/water 95/5. A gradient was run from 10% B to 100% B in 10 min, stay at 100% B for 1 min, re-equilibrate for 6 min. System was operated at 1 mL/min.

Procedure 2 (AP2):

[0242] The analysis was performed on a combined prep/analytical Waters/Micromass system consisting of a ZMD single quadropole mass spectrometer equipped with electro-spray ionization interface. The HPLC system consisted of a Waters 600 gradient pump with on-line degassing, a 2700 sample manager and a 996 PDA detector.

[0243] Separation was performed on an X-Terra MS C18, 5 μ m 4.6x50mm column. Buffer A: 10 mM ammoniumacetate in water, buffer B: 10 mM ammoniumacetate in acetonitrile/water 95/5. A gradient was run from 30% B to 100% B in 7 min, stay at 100% B for 1 min, re-equilibrate for 5.5 min. System was operated at 1 ml/min.

General synthetic procedures

General synthetic procedure 1 (GP1)

5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (II)

[0244] Diltiazem hydrochloride (90 mg, 0.2 mmol) was taken up in THF (1 mL) and mixed with LiOH (14 mg, 0.6 mmol) in water (0.5 mL) in a vial. The mixture was heated in the MW at 160 °C for 5 min, then drawn in on celite and purified by flash chromatography (DCM/MeOH 9:1) to yield the title compound as a clear oil (70 mg, 94%). UV/MS: 100/100. ¹H NMR (400 MHz, CD₃OD) δ 7.74 (dd, *J* = 7.8 Hz and 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.43 (dt, *J* = 8.7 Hz and 2.0, 2H), 7.36 (td, *J* = 7.4 Hz and 1.6 Hz, 1H), 6.92 (dt, *J* = 8.7 Hz and 2.0 Hz, 2H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.56-4.49 (m, 1H), 4.35 (d, *J* = 7.2 Hz, 1H), 3.88-3.82 (m, 1H), 3.81 (s, 3H), 2.98-2.92 (m, 1H), 2.69-2.62 (m, 1H), 2.39 (s, 6H). ¹³C NMR (100 MHz, CD₃OD), δ 170.6, 158.7, 143.7, 133.7, 129.9, 129.5, 127.6, 126.4, 125.5, 123.1, 111.9, 67.9, 55.3, 54.4, 53.2, 45.0, 42.2.

General synthetic procedure 2 (GP2)

5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (IV)

[0245] Diltiazem hydrochloride (90 mg, 0.2 mmol) in a vial was taken up in HBr (48%, 5 mL) and heated to 100 °C for 30 min. The reaction mixture was concentrated *in vacuo*, redissolved in MeOH and drawn in on celite. Then purified by flash chromatography (DCM/MeOH 9:1) to yield the title compound as a clear oil (69 mg, 96%). UV/MS: 97/100. ¹H NMR (400 MHz, DMSO) δ: 7.71 (d, *J* = 8.0 Hz, 1H), 7.62-7.58 (m, 2H), 7.39-7.35 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 4.81 (d, *J* = 7.4 Hz, 1H), 4.67 (bd, *J* = 7.0 Hz, 1H), 4.46-4.41 (m, 1H), 4.21 (t, *J* = 6.7 Hz, 1H), 4.01 (s, 3H), 3.14-3.09 (m, 1H), 2.80 (s, 6H).

General synthetic procedure 3 (GP3)

2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (I)

[0246] Diltiazem hydrochloride (90 mg, 0.2 mmol) was freebased (taken up in EtOAc 5 mL, washed with NaHCO₃ 2 x 3 mL, dried over Na₂SO₄ and concentrated *in vacuo*), and then taken up in toluene. Trichloroethylchloroformate (36 µL, 0.26 mmol) was added and the reaction mixture heated in the MW at 180 °C for 15 min. The crude was then concentrated *in vacuo* and redissolved in glacial acetic acid (2.5 mL). Zinc dust (20 mg, 0.3 mmol) was added and the reaction mixture heated to 50 °C for 24 h, additional Zinc dust (25 mg, 0.38 mmol) was added and the heating was continued for another 2 h. The reaction mixture was cooled and filtered, the filtrate was concentrated *in vacuo* and the residue dissolved in EtOAc (5 mL), washed with saturated NaHCO₃ (2 x 3 mL) and dried over Na₂SO₄ and concentrated *in vacuo*. Purified by flash chromatography (DCM/MeOH 9:1) to yield the title compound as a clear oil (64 mg, 80%). UV/MS: 85/76. ¹H NMR (400 MHz, CD₃OD) δ: 7.79 (dd, *J* = 7.4 Hz and 1.4, 1H), 7.69-7.63 (m, 2H), 7.45-7.40 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.11 (s, 2H), 4.41-4.36 (m, 1H), 4.22-4.15 (m, 1H), 3.81 (s, 3H), 3.55-3.49 (m, 1H), 3.32-3.24 (m, 1H), 2.79 (s, 3H), 1.87 (s, 3H).

General synthetic procedure 4 (GP4)

3-hydroxy-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (III)

[0247] Diltiazem hydrochloride (90 mg, 0.2 mmol) was freebased (taken up in EtOAc 5 mL, washed with NaHCO₃ 2 x 3 mL, dried over Na₂SO₄ and concentrated *in vacuo*), and then taken up in dichloroethane (2 mL) and cooled to 0 °C, before adding 1-chloroethyl chloroformate (135 µL, 1.25 mmol). The reaction mixture was left at 0 °C for 10 min then heated to 180 °C on the MW for 15 min. After cooling to room temperature the solvent was evaporated off to yield an oil. The oil was dissolved in dichloroethane (1 mL) before dropwise addition of ethanol (1 mL). The solution was heated to 80 °C over night then cooled to room temperature and concentrated. The residue was taken up in diethyl ether (10

mL) and washed with 1 N NaOH (5 mL) and water (5 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purified by flash chromatography (DCM/MeOH 9:1) to yield the title compound as a white solid (67 mg, 94%). UV/MS: 100/100. ¹H NMR (400 MHz, CD₃OD) δ : 7.74 (dd, J = 7.8 Hz and 1.3 Hz, 1H), 7.59-7.52 (m, 2H), 7.38-7.32 (m, 3H), 6.90 (td, J = 8.8 Hz and 1.9 Hz, 2H), 4.92 (d, J = 7.4 Hz, 1H), 4.67-4.59 (m, 1H), 4.33 (d, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.79-3.73 (m, 1H), 2.85 (t, J = 6.8 Hz, 2H), 2.38 (s, 3H). ¹³C NMR (100 MHz, CD₃OD) δ : 172.2, 160.3, 145.1, 135.1, 131.2, 131.0, 128.9, 127.9, 126.8, 124.8, 113.4, 69.4, 56.8, 54.6, 48.5, 47.2, 34.3.

General synthetic procedure 5 (GP5)

5-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (V)

[0248] 2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (172 mg, 0.5 mmol), *N*-(2-Bromoethyl)phthalimide (254 mg, 1 mmol) and Cs₂CO₃ (178 mg, 0.55 mmol) was taken up in MeCN (3 mL) and heated to 180 °C on the MW for 25 min. The cooled reaction mixture was taken up in EtOAc (10 mL) and washed with water (2 x 5 mL), then dried over Na₂SO₄ and concentrated *in vacuo*. Purified by flash chromatography (Heptane/EtOAc 2:1) to yield the title product as a white solid (200 mg, 78%). UV/MS: 94/72.

General synthetic procedure 6 (GP6)

5-(2-aminoethyl)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VI)

[0249] 5-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (150 mg, 0.3 mmol) was taken up in absolute ethanol (2 mL). Methylamine 33% in ethanol (4 mL) was added at room temperature, the reaction mixture was left for 5 more min at this temperature before heating to reflux for 2.5 h. After cooling to room temperature the crude was concentrated and purified by SCX to yield the title compound as an oil (62 mg, 62%). UV/MS: 81/65.

General synthetic procedure 7 (GP7)

2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5H)-one (VII)

[0250] 3-hydroxy-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (179 mg, 0.5 mmol) in 48% HBr (5 mL) was reacted according to GP2. After chromatography (DCM/MeOH 9:1) the title compound was obtained as an oil (9.6 mg, 6%). UV/MS: 100/36.

General synthetic procedure 8 (GP8)

5-(2-aminoethyl)-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-1,5-benzo-thiazepin-4(5H)-one (VIII)

[0251] In a dry argon flushed schlenk flask 5-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (26 mg, 0.05 mmol) was taken up in dry DCM (0.5 mL), then cooled to -70 °C in a dry ice/isopropanol bath before slowly adding BBr₃ (1 M in DCM, 125 µL, 0.13 mmol). The reaction mixture was allowed to warm to room temperature over 30 min, then it was poured into ice water and stirred for another 30 min. The reaction intermediate was extracted with DCM, dried over Na₂SO₄ and concentrated *in vacuo*. The intermediate was then taken up in hydrazine in MeOH (0.2 M, 2 mL, 0.4 mmol) and left at room temperature over night. Concentrated *in vacuo*, then taken up in EtOAc (5 mL) and extracted with 2 N NaOH (2 x 3 mL). The aqueous phases were made acidic with 2 N HCl and back extracted with EtOAc (2 x 3 mL). The organic phases were combined, dried over Na₂SO₄ and concentrated *in vacuo* to yield the title compound as an oil (0.8 mg, 5%). UV/MS: 97/100.

General synthetic procedure 9 (GP9)

3-(acetyloxy)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepine-5-propanoic acid methyl ester (8) 161aej61c

[0252] 2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (172 mg, 0.5 mmol), methyl 3-bromopropionate (167 mg, 1 mmol) and Cs₂CO₃ (178

mg, 0.55 mmol) in MeCN (3 mL) was reacted according to GP5. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as an oil (138 mg, 64%). UV/MS: 100/98.

General synthetic procedure 10 (GP10)

2,3,4,5-tetrahydro-3-hydroxy-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepine-5-propanoic acid (9) 161aej64

[0253] 3-(acetyloxy)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepine-5-propanoic acid methyl ester (134 mg, 0.3 mmol) and LiOH (43 mg, 1.8 mmol) in THF (1 mL) and water (1 mL) was reacted according to GP1. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as a solid (84 mg, 75%). UV/MS: 94/90. ¹H NMR (400 MHz, CD₃OD) δ: 7.74 (dd, *J* = 7.6 Hz and 1.6 Hz, 1H), 7.59-7.48 (m, 2H), 7.40-7.35 (m, 3H), 6.88 (td, *J* = 8.8 Hz and 1.8 Hz, 2H), 5.41-5.35 (m, 1H), 4.14-4.34 (m, 1H), 3.78 (s, 3H), 1.99 (d, *J* = 7.6 Hz, 2H), 1.32 (d, *J* = 7.6 Hz, 2H). ¹³C NMR (100 MHz, CD₃OD) δ: 173.9, 172.0, 160.2, 142.9, 135.2, 131.4, 131.3, 128.3, 126.9, 125.8, 113.4, 69.8, 56.5, 55.0, 54.6, 14.4.

General synthetic procedure 11 (GP11)

3-(acetyloxy)-2,3-dihydro-5-(2-hydroxyethyl)-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (10) 161aej61d

[0254] 2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (172 mg, 0.5 mmol), 2-bromoethanol (125 mg, 1 mmol) and Cs₂CO₃ (178 mg, 0.55 mmol) in MeCN (3 mL) was reacted according to GP5. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as an oil (11 mg, 6%). UV/MS: 98/99.

General synthetic procedure 12 (GP12)

3-(acetyloxy)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepine-5-acetonitrile (11) 161aej55

[0255] 2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (172 mg, 0.5 mmol), iodoacetonitrile (167 mg, 1 mmol) and Cs₂CO₃ (178 mg, 0.55 mmol) in MeCN (3 mL) was reacted according to GP5. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as an oil (12 mg, 6%). UV/MS: 90/72.

General synthetic procedure 13 (GP13)

3-(acetyloxy)-5-(2,1,3-benzoxadiazol-5-ylmethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (12) 161aej61b

[0256] 2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate (172 mg, 0.5 mmol), methyl 5-(bromomethyl)benzofurazan (213 mg, 1 mmol) and Cs₂CO₃ (178 mg, 0.55 mmol) in MeCN (3 mL) was reacted according to GP5. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as a white solid (173 mg, 73%). UV/MS: 96/78. ¹H NMR (400 MHz, CDCl₃) δ: 7.82-7.78 (m, 2H), 7.71 (dd, *J* = 7.6 Hz and 1.6 Hz, 1H), 7.50 (dd, *J* = 9.2 Hz and 1.4 Hz, 1H), 7.45 (dd, *J* = 7.4 Hz and 1.7 Hz, 1H), 7.39-7.36 (m, 3H), 7.27 (dt, *J* = 7.4 Hz and 1.4 Hz, 1H), 6.88-6.86 (m, 2H), 5.37 (dd, *J* = 15.8 Hz and 1.0 Hz, 1H), 5.27 (d, *J* = 7.6 Hz, 1H), 5.13 (dd, *J* = 15.8 Hz and 1.0 Hz, 1H), 5.04 (d, *J* = 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 170.2, 168.0, 160.1, 149.4, 148.9, 145.1, 141.1, 136.1, 132.7, 131.4, 130.9, 128.5, 128.2, 124.1, 116.8, 114.6, 114.1, 71.4, 55.5, 54.8, 52.9, 20.7.

General synthetic procedure 14 (GP14)

5-(2,1,3-benzoxadiazol-5-ylmethyl)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (13) 161aej65

[0257] 3-(acetyloxy)-5-(2,1,3-benzoxadiazol-5-ylmethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (50 mg, 0.1 mmol) and LiOH (7 mg, 0.3 mmol) in THF (0.5 mL) and water (0.5 mL) was reacted according to GP1. After chromatography (heptane/EtOAc 2:1) the title compound was obtained as a solid (39 mg, 90%). UV/MS: 98/100.

Literature Cited

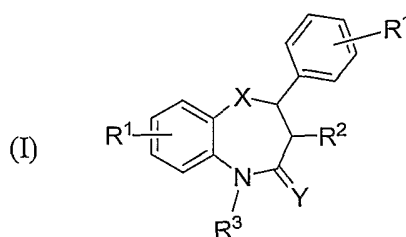
[0258] The following references are cited herein and are incorporated by reference herein in their entirety, including any drawings.

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WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of diltiazem or a diltiazem analog for the production of a medicament for the treatment of a ghrelin receptor related disease or disorder comprising identifying a subject in need thereof, wherein the disease or disorder is selected from the group consisting of: an eating disorder, a wasting disorder, promotion of weight gain, a gastrointestinal disorder, a cardiovascular disorder, a sleep disorder, cancer, hormone deficiencies, dwarfism, somatopause, catabolic states, osteoporosis, disorders of the pancreas, diabetes, control of glucose levels, anxiety disorders, memory loss, memory impairment, a cognitive deficit, a neurodegenerative disorder and an inflammatory disorder, wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl

optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR₅, C(R₅)₂,

Wherein R₅ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted,

C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

2. The use of claim 1, wherein the eating disorder is selected from the group consisting of anorexia nervosa, bulimia, cachexia and cancer cachexia.

3. The use of claim 1, wherein the wasting disorder is selected from the group consisting of wasting, HIV induced wasting, AIDS related cachexia, wasting associated with surgical stress, cachexia of critical illness, wasting associated with sepsis, wasting associated with glucocorticoid administration, wasting associated with cancer and other catabolic states.

4. The use of claim 1, wherein the promotion of weight gain comprises reversing catabolic states.

5. The use of claim 1, wherein the gastrointestinal disorder is selected from the group consisting of reduced gastric and intestinal motility, post-operative gastric ileus, delayed gastric emptying, delayed gastric emptying due to diabetes, delayed gastric emptying post-operatively, short bowel syndrome and a gastric ulcer.

6. The use of claim 1, wherein the cardiovascular disorder is selected from the group consisting of angina, cardiac ischemia, cardiac failure, hypertension, atherosclerosis, and hypotension.

7. The use of claim 1, wherein the sleep disorder is selected from the group consisting of insomnia, narcolepsy, catalepsy, somnolence, daytime somnolence, improving sleep architecture and facilitating induction of sleep.

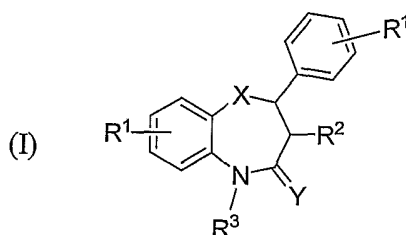
8. The use of claim 1, wherein the hormone deficiency is a deficiency in producing a hormone selected from the group consisting of growth hormone, ACTH, cortisol, insulin-like growth factor 1 (IGF-1), and prolactin

9. The use of claim 1, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Amyotrophic Lateral Sclerosis (ALS) and multiple sclerosis.

10. The use of claim 1, wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis and atherosclerosis.

11. Use of a therapeutically effective amount of diltiazem or a diltiazem analog for the production of a medicament for promoting weight gain in a subject in need thereof,

wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR_5 , $C(R_5)_2$,

Wherein R_5 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or

branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted;
or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

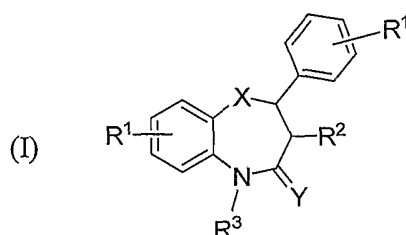
Y is oxygen or sulfur.

12. The use of claim 11, wherein said subject is a human.

13. The use of claim 11, wherein said subject is a domesticated animal useful for producing meat, milk, fish or eggs.

14. The use of claim 11, wherein said subject is a domesticated fowl, bovine, ovine, caprine, or porcine animal.

15. Use of a therapeutically effective amount of diltiazem or a diltiazem analog for the production of a medicament for controlling the appetite of a subject in need thereof, wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR_5 , $C(R_5)_2$,

Wherein R_5 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl

optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

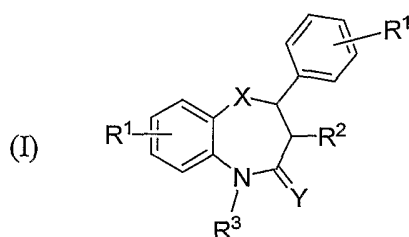
R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

16. The use of claim 15, wherein said subject is a human.
17. The use of claim 15, wherein said subject is a domesticated animal useful for producing meat, milk, fish or eggs.
18. The use of claim 15, wherein said subject is a domesticated fowl, bovine, ovine, caprine, or porcine animal.
19. A method of increasing food production comprising identifying a subject in need thereof and administering to said subject a therapeutically effective amount of diltiazem or a diltiazem analog to stimulate the appetite of said subject, wherein said increased food production is by promoting weight gain, increasing appetite, or treating an eating disorder requiring appetite stimulation,

wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl

optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR₅, C(R₅)₂,

Wherein R₅ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted,

C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

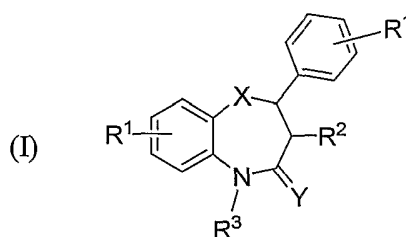
Y is oxygen or sulfur.

20. The method of claim 19, wherein said subject is a domesticated animal useful for producing meat, milk, fish or eggs.

21. The method of claim 19, wherein said subject is a domesticated fowl, bovine, ovine, caprine, or porcine animal.

22. A method of treating a ghrelin receptor related disease or disorder comprising identifying a subject in need thereof and administering to said subject a therapeutically effective amount of diltiazem or a diltiazem analog, wherein the disease or disorder is selected from the group consisting of: an eating disorder, a wasting disorder, promotion of weight gain, a gastrointestinal disorder, a cardiovascular disorder, a sleep disorder, cancer, hormone deficiencies, dwarfism, somatopause, catabolic states, osteoporosis, disorders of the pancreas, diabetes, control of glucose levels, anxiety disorders, memory loss, memory impairment, a cognitive deficit, a neurodegenerative disorder and an inflammatory disorder,

wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R₁ may be present 0-9 times and each R₁ is independently selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₄, -N(R₄)₂, -CN,

$-\text{C}(=\text{Z})\text{R}_4$, $-\text{C}(=\text{Z})\text{OR}_4$, $-\text{C}(=\text{Z})\text{N}(\text{R}_4)_2$, $-\text{N}(\text{R}_4)-\text{C}(=\text{Z})\text{R}_4$,
 $-\text{N}(\text{R}_4)-\text{C}(=\text{Z})\text{N}(\text{R}_4)_2$, $-\text{OC}(=\text{Z})\text{R}_4$, and $-\text{SR}_4$, $-\text{SOR}_4$, $-\text{SO}_2\text{R}_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR_5 , $\text{C}(\text{R}_5)_2$,

Wherein R_5 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted;
 or

two R_5 and the X may form C_3 - C_7 cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R_2 is selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-\text{OR}_6$, $-\text{N}(\text{R}_6)_2$, $-\text{CN}$,
 $-\text{C}(=\text{Z})\text{R}_6$, $-\text{C}(=\text{Z})\text{OR}_6$, $-\text{C}(=\text{Z})\text{N}(\text{R}_6)_2$, $-\text{N}(\text{R}_6)-\text{C}(=\text{Z})\text{R}_6$,
 $-\text{N}(\text{R}_6)-\text{C}(=\text{Z})\text{N}(\text{R}_6)_2$, $-\text{OC}(=\text{Z})\text{R}_6$, and $-\text{SR}_6$, $-\text{SOR}_6$, $-\text{SO}_2\text{R}_6$,

wherein Z is oxygen or sulfur; and wherein each R_6 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted.

optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

23. The method of claim 22, wherein the eating disorder is selected from the group consisting of anorexia nervosa, bulimia, cachexia and cancer cachexia.

24. The method of claim 22, wherein the wasting disorder is selected from the group consisting of wasting, HIV induced wasting, AIDS related cachexia, wasting associated with surgical stress, cachexia of critical illness, wasting associated with sepsis, wasting associated with glucocorticoid administration, wasting associated with cancer and other catabolic states.

25. The method of claim 22, wherein the promotion of weight gain comprises reversing catabolic states.

26. The method of claim 22, wherein the gastrointestinal disorder is selected from the group consisting of reduced gastric and intestinal motility, post-operative gastric ileus, delayed gastric emptying, delayed gastric emptying due to diabetes, delayed gastric emptying post-operatively, short bowel syndrome and a gastric ulcer.

27. The method of claim 22, wherein the cardiovascular disorder is selected from the group consisting of angina, cardiac ischemia, cardiac failure, hypertension, atherosclerosis, and hypotension.

28. The method of claim 22, wherein the sleep disorder is selected from the group consisting of insomnia, narcolepsy, catalepsy, somnolence, daytime somnolence, improving sleep architecture and facilitating induction of sleep.

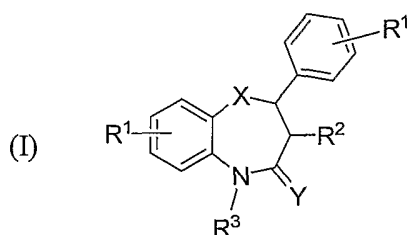
29. The method of claim 22, wherein the hormone deficiency is a deficiency in producing a hormone selected from the group consisting of growth hormone, ACTH, cortisol, insulin-like growth factor 1 (IGF-1), and prolactin

30. The method of claim 22, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Amyotrophic Lateral Sclerosis (ALS) and multiple sclerosis.

31. The method of claim 22, wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis and atherosclerosis.

32. A method of promoting weight gain comprising identifying a subject in need thereof and administering to the subject a therapeutically effective amount of diltiazem or a diltiazem analog,

wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R_4 is independently selected from the group consisting of hydrogen,

C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR₅, C(R₅)₂,

Wherein R₅ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1 - C_5 straight chained or branched alkyl optionally substituted, C_2 - C_5 straight chained or branched alkenyl optionally substituted, C_2 - C_5 straight chained or branched alkynyl optionally substituted, C_3 - C_7 cycloalkyl, and C_5 - C_{10} cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

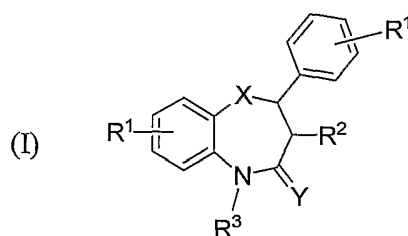
33. The method of claim 32, wherein said subject is a human.

34. The method of claim 32, wherein said subject is a domesticated animal useful for producing meat, milk, fish or eggs.

35. The method of claim 32, wherein said subject is a domesticated fowl, bovine, ovine, caprine, or porcine animal.

36. A method of controlling the appetite of a subject comprising identifying a subject in need thereof and administering to the subject a therapeutically effective amount of a diltiazem or a diltiazem analog,

wherein said diltiazem analog is a compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 may be present 0-9 times and each R_1 is independently selected from the group consisting of C_1 - C_4 straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, $-OR_4$, $-N(R_4)_2$, $-CN$, $-C(=Z)R_4$, $-C(=Z)OR_4$, $-C(=Z)N(R_4)_2$, $-N(R_4)-C(=Z)R_4$, $-N(R_4)-C(=Z)N(R_4)_2$, $-OC(=Z)R_4$, and $-SR_4$, $-SOR_4$, $-SO_2R_4$,

wherein Z is oxygen or sulfur; and wherein each R₄ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

X is selected from the group consisting of oxygen, sulfur, NR₅, C(R₅)₂,

Wherein R₅ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted; or

two R₅ and the X may form C₃-C₇ cycloalkyl, heterocyclic ring, aryl, or heteroaryl ring optionally substituted.

R₂ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₆, -N(R₆)₂, -CN, -C(=Z)R₆, -C(=Z)OR₆, -C(=Z)N(R₆)₂, -N(R₆)-C(=Z)R₆, -N(R₆)-C(=Z)N(R₆)₂, -OC(=Z)R₆, and -SR₆, -SOR₆, -SO₂R₆,

wherein Z is oxygen or sulfur; and wherein each R₆ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted.

R₃ is selected from the group consisting of C₁-C₄ straight chained or branched alkyl optionally substituted, cycloalkyl, aryl or heteroaryl optionally substituted, -C(=Z)R₇, -C(=Z)OR₇, and -C(=Z)N(R₇)₂,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted, C₂-C₅ straight chained or branched alkenyl optionally substituted, C₂-C₅ straight chained or branched alkynyl optionally substituted, C₃-C₇ cycloalkyl, and C₅-C₁₀ cycloalkenyl, aryl or heteroaryl optionally substituted, and

Y is oxygen or sulfur.

37. The method of claim 36, wherein said subject is a human.
38. The method of claim 36, wherein said subject is a domesticated animal useful for producing meat, milk, fish or eggs.
39. The method of claim 36, wherein said subject is a domesticated fowl, bovine, ovine, caprine, or porcine animal.

Figure 1

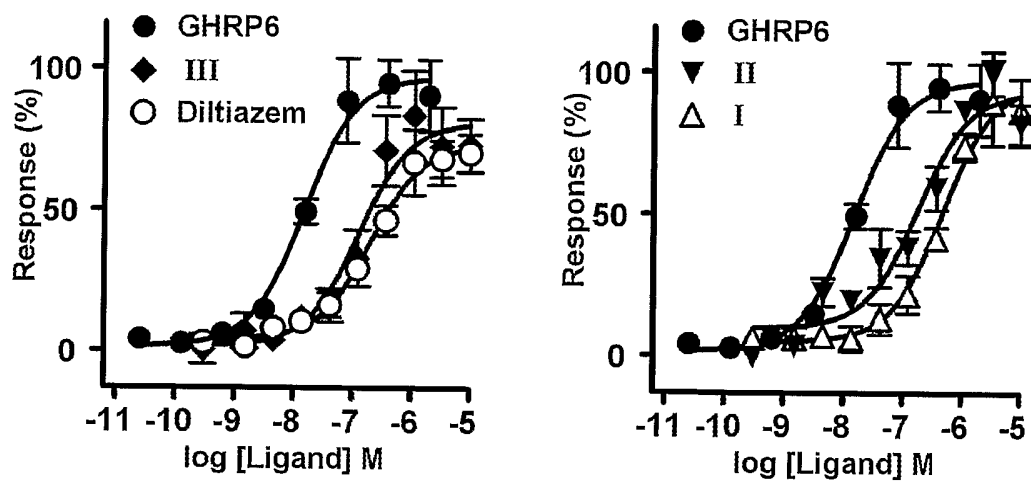


Figure 2

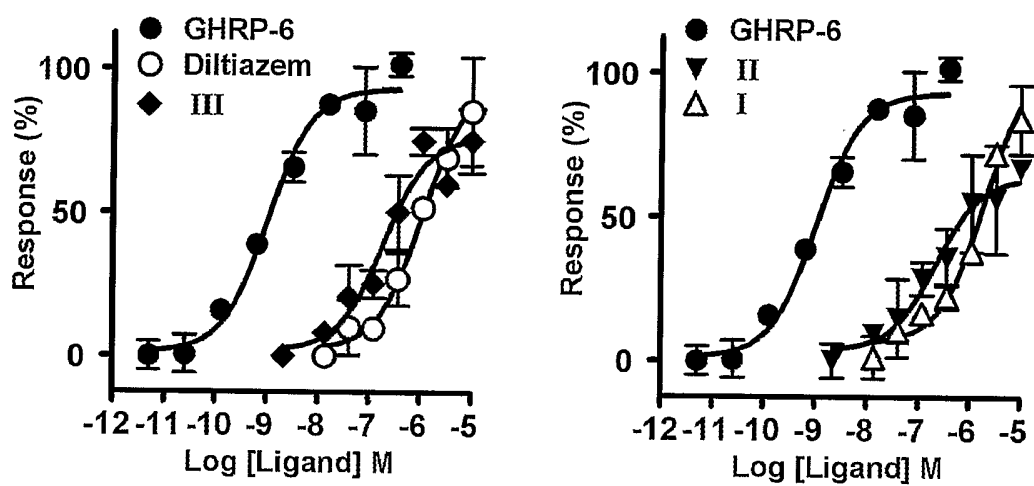


Figure 3

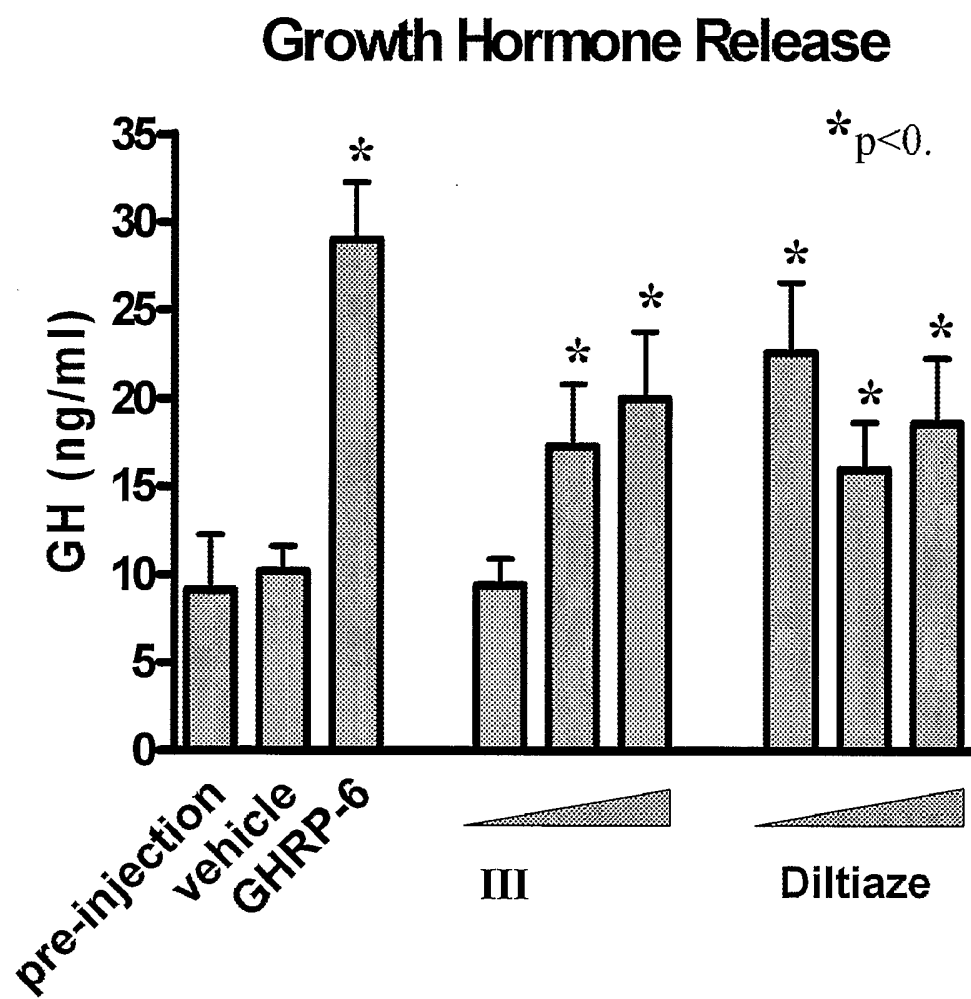


Figure 4

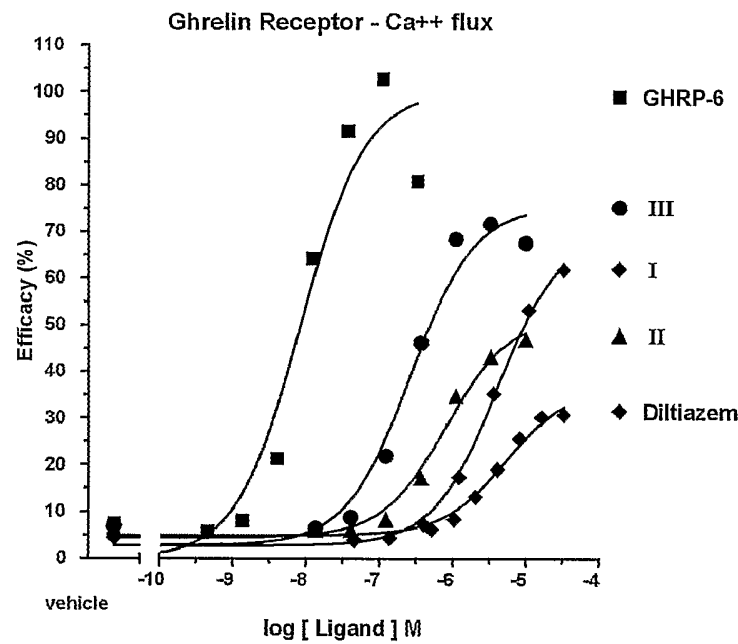
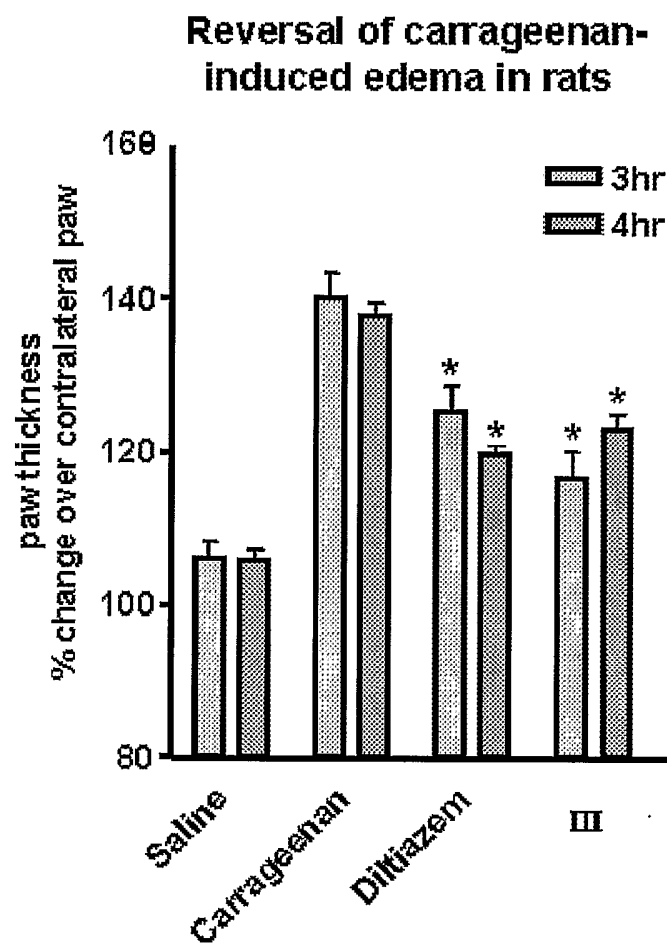


Figure 5



*p<0.05 indicating significant difference from carrageenan

Animals were dosed i.p. with 10 mg/kg of the indicated compounds.

Figure 6

