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(54) SUBSTITUTED ACYLANILIDES AND METHODS OF USE THEREOF

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- **KIM ET AL: "The para substituent of S-3-(phenoxy)-2-hydroxy-2-methyl-N-(4-nitr o-3-trifluoromethyl-phenyl)-propionamides is a major structural determinant of in vivo disposition and activity of selective androgen receptor modulators", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS , 315(1), 230-239 CODEN: JPETAB; ISSN: 0022-3565,, 1 January 2005 (2005-01-01), XP002609516,**

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Description**FIELD OF THE INVENTION**

5 [0001] This invention provides substituted acylanilide compounds and uses thereof in treating a variety of diseases or conditions in a subject, including, *inter-alia*, a muscle wasting disease and/or disorder or a bone-related disease and/or disorder

BACKGROUND OF THE INVENTION

10 [0002] The nuclear hormone receptor superfamily is one of the largest classes of transcription factors and is involved in abundant physiological processes. The 48 members of this family are divided into three classes with class 1 comprised of receptors for androgens (AR), estrogens (ER- α and ER- β), glucocorticoids (GR), progesterone (PR) and mineralo-corticoids (MR). Class 2 contains receptors for retinoids, thyroids and vitamin D, while class 3 includes receptors for which ligands are yet to be identified (orphans). Nuclear hormone receptors have an N-terminal domain (NTD) whose function is less characterized, a DNA binding domain (DBD) which is responsible for the binding of receptor to DNA response elements, a hinge region that contains the nuclear localization signal and a ligand binding domain (LBD) to which ligands bind and activate or inhibit receptor action. In addition, there are two activation function domains, one in the NTD (AF-1) and the other in the LBD (AF-2). Due to the high amino acid sequence homology of the DBD, moderate homology and similar secondary and tertiary structural features of the LBD, and common chemical features of steroidal ligands, class I receptors are often capable of binding (i.e., cross reacting) with the ligands of other class I receptors. For example, early studies with AR and ER suggest that the orientation of the steroid in the LBD, with the steroid A-ring in contact with helix-3 and the D-ring in contact with helix-11 residues, is likely to be general for all the steroid hormone receptors.

25 [0003] The androgen receptor ("AR") is a ligand-activated transcriptional regulatory protein that mediates induction of male sexual development and function through its activity with endogenous androgens. Androgens are generally known as the male sex hormones. The androgenic hormones are steroids which are produced in the body by the testes and the cortex of the adrenal gland or can be synthesized in the laboratory. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone mass, prostate growth, spermatogenesis, and the male hair pattern (Matsumoto, *Endocrinol. Met. Clin. N. Am.* 23:857-75 (1994)). The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal steroid secreted by the testes and is the primary circulating androgen found in the plasma of males. Testosterone is converted to DHT by the enzyme 5 alpha-reductase in many peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most androgen actions (Zhou, et al., *Molec. Endocrinol.* 9:208-18 (1995)). Other steroidal androgens include esters of testosterone, such as the cypionate, propionate, phenylpropionate, cyclopentylpropionate, isocarporate, enanthate, and decanoate esters, and other synthetic androgens such as 7-Methyl-Nortestosterone ("MENT") and its acetate ester (Sundaram et al., "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," *Ann. Med.*, 25:199-205 (1993). Because the AR is involved in male sexual development and function, the AR is a likely target for effecting male contraception or other forms of hormone replacement therapy. Publications that describe selective androgen receptor modulators (SARMs) include US 2005/038110 A1, US 2006/035965 A1, Kim et al., (2005) *J. Pharmacol. Exp. Ther.* 315(1), 230-239, and WO 98/55153 A1.

35 [0004] The human progesterone receptor (PR) occurs as three different isoforms: PR-A, PR-B, and PR-C (Kastner et al., *EMBO J* 9:1603-1614, 1990; Wei et al., *Mol Endo* 10:1379-1387, 1996), of which PR-A and PR-B are the most abundant. However, the ratio of PR-A vs. PR-B isoforms is not constant among target tissues, and this can alter the cellular response, because the activity of each isoform can vary.

45 [0005] There are very few compounds that exhibit partial progestin activity under a wide variety of conditions. RU-486, the most commonly used antiprogestin, displays partial agonist activity only under selected conditions. Antiprogestin compounds with partial agonist activity are useful for treating various progestin-regulated diseases and conditions, however, the few known antiprogestins have only limited partial agonist activity, and there remains a need in the art for antiprogestins with broad-range partial agonist activity.

50 [0006] Worldwide population growth and social awareness of family planning have stimulated a great deal of research in contraception. Contraception is a difficult subject under any circumstance. It is fraught with cultural and social stigma, religious implications, and, most certainly, significant health concerns. This situation is only exacerbated when the subject focuses on male contraception. Despite the availability of suitable contraceptive devices, historically, society has looked to women to be responsible for contraceptive decisions and their consequences. Although concern over sexually transmitted diseases has made men more aware of the need to develop safe and responsible sexual habits, women still often bear the brunt of contraceptive choice. Women have a number of choices, from temporary mechanical devices such as sponges and diaphragms to temporary chemical devices such as spermicides. Women also have at their disposal more

permanent options, such as physical devices including IUDs and cervical caps as well as more permanent chemical treatments such as birth control pills and subcutaneous implants. However, to date, the only options available for men include the use of condoms and vasectomy. Condom use, however is not favored by many men because of the reduced sexual sensitivity, the interruption in sexual spontaneity, and the significant possibility of pregnancy caused by breakage or misuse. Vasectomies are also not favored. If more convenient methods of birth control were available to men, particularly long-term methods which require no preparative activity immediately prior to a sexual act, such methods could significantly increase the likelihood that men would take more responsibility for contraception.

[0007] Administration of the male sex steroids (e.g., testosterone and its derivatives) has shown particular promise in this regard due to the combined gonadotropin-suppressing and androgen-substituting properties of these compounds (Steinberger et al., "Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive, Fertility and Sterility 28:1320- 28 (1977)). Chronic administration of high doses of testosterone completely abolishes sperm production (azoospermia) or reduces it to a very low level (oligospermia). The degree of spermatogenic suppression necessary to produce infertility is not precisely known. However, a recent report by the World Health Organization showed that weekly intramuscular injections of testosterone enanthate result in azoospermia or severe oligospermia (i.e., less than 3 million sperm per ml) and infertility in 98% of men receiving therapy (World Health Organization Task Force on Methods And Regulation of Male Fertility, "Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," Fertility and Sterility 65:821-29 (1996)).

[0008] A variety of testosterone esters have been developed which are more slowly absorbed after intramuscular injection and thus result in greater androgenic effect. Testosterone enanthate is the most widely used of these esters. While testosterone enanthate has been valuable in terms of establishing the feasibility of hormonal agents for male contraception, it has several drawbacks, including the need for weekly injections and the presence of supraphysiologic peak levels of testosterone immediately following intramuscular injection (Wu, "Effects of Testosterone Enanthate in Normal Men: Experience From a Multicenter Contraceptive Efficacy Study," Fertility and Sterility 65:626-36 (1996)).

[0009] Bone mineral density (BMD) decreases with age in both males and females. Decreased amounts of bone mineral content (BMC) and BMD correlate with decreased bone strength and predispose patients to fracture.

[0010] Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated. The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study estimated that there will be 4.5 million hip fractures worldwide in 2050.

[0011] Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake. However, osteoporosis also occurs frequently in males. It is well established that the bone mineral density of males decrease with age. Decreased amounts of bone mineral content and density correlates with decreased bone strength, and predisposes to fracture. The molecular mechanisms underlying the pleiotropic effects of sex-hormones in non-reproductive tissues are only beginning to be understood, but it is clear that physiologic concentrations of androgens and estrogens play an important role in maintaining bone homeostasis throughout the life-cycle. Consequently, when androgen or estrogen deprivation occurs there is a resultant increase in the rate of bone remodeling that tilts the balance of resorption and formation to the favor of resorption that contributes to the overall loss of bone mass. In males, the natural decline in sex-hormones at maturity (direct decline in androgens as well as lower levels of estrogens derived from peripheral aromatization of androgens) is associated with the frailty of bones. This effect is also observed in males who have been castrated.

[0012] Muscle wasting refers to the progressive loss of muscle mass and/or to the progressive weakening and degeneration of muscles, including the skeletal or voluntary muscles, which control movement, cardiac muscles, which control the heart (cardiomyopathics), and smooth muscles. Chronic muscle wasting is a chronic condition (i.e. persisting over a long period of time) characterized by progressive loss of muscle mass, weakening and degeneration of muscle.

[0013] The loss of muscle mass that occurs during muscle wasting can be characterized by muscle protein degradation by catabolism. Protein catabolism occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Muscle protein catabolism, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting.

[0014] Muscle wasting is associated with chronic, neurological, genetic or infectious pathologies, diseases, illnesses or conditions. These include muscular dystrophies such as Duchenne muscular dystrophy and myotonic dystrophy; muscle atrophies such as post-polio muscle atrophy (PPMA); cachexias such as cardiac cachexia, aids cachexia and cancer cachexia, malnutrition, leprosy, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), cancer,

end stage renal failure, sarcopenia, emphysema, osteomalacia, HIV infection, AIDS, and cardiomyopathy.

[0015] In addition, other circumstances and conditions are linked to and can cause muscle wasting. These include chronic lower back pain, advanced age, central nervous system (CNS) injury, peripheral nerve injury, spinal cord injury, chemical injury, central nervous system (CNS) damage, peripheral nerve damage, spinal cord damage, chemical damage, burns, disuse deconditioning that occurs when a limb is immobilized, long term hospitalization due to illness or injury, and alcoholism.

[0016] An intact androgen receptor (AR) signaling pathway is crucial for appropriate development of skeletal muscles. Furthermore, an intact AR-signaling pathway increases lean muscle mass, muscle strength and muscle protein synthesis.

[0017] Muscle wasting, if left unabated, can have dire health consequences. For example, the changes that occur during muscle wasting can lead to a weakened physical state that is detrimental to an individual's health, resulting in increased susceptibility to bone fracture and poor physical performance status. In addition, muscle wasting is a strong predictor of morbidity and mortality in patients suffering from cachexia and AIDS.

[0018] New innovative approaches are urgently needed at both the basic science and clinical levels to develop compounds which are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with androgen deficiency in a female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of chronic muscular wasting or sarcopenia; e) decreasing the incidence of, halting or causing a regression of prostate cancer; f) oral androgen replacement and/or other clinical therapeutic and/or diagnostic areas.

[0019] A wide variety of diseases and/or conditions are affected by hypogonadism, and catabolic effects, including kidney disease, central nervous system injuries, burns and chronic wounds.

[0020] In the United States (US), there is a rising incidence and prevalence of kidney failure. The number of patients enrolled in end-stage renal disease (ESRD) Medicare-funded programs has increased from approximately 10,000 beneficiaries in 1973 to 86,354 in 1983, and to 431,284 as of December 31, 2002. In 2002 alone, 100,359 patients entered the US ESRD program. Chronic kidney disease (CKD) is a precursor to ESRD and occurs when the kidneys are not able to adequately remove wastes from the body. CKD is a slowly progressing disease, in which diabetes, hypertension and anemia may be co-morbid conditions.

[0021] CKD is diagnosed using a staging system that demonstrates the amount of kidney function available (stage 1 = normal kidney function) and patients often do not present symptoms in the early stages. Stage 5 of CKD is ESRD, which is a complete or near complete failure of the kidneys and usually occurs when kidney function is less than 10% of baseline.

[0022] Accompanying symptoms associated with ESRD include hypogonadism, involuntary weight loss, fatigue and others.

[0023] Burns result in a testosterone reduction, nitrogen level reduction and a reduction in bone mineral density (BMD), which may persist even as long as one year following the injury and is associated with impaired wound healing, increased infection risks, erosion of lean body mass, hampered rehabilitation, and delayed reintegration of burn survivors into society. Catabolic effects initiated as a result of the burn lead to significant involuntary weight loss, further compounding the problem.

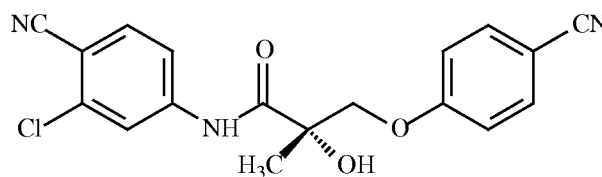
[0024] Spinal cord injuries (SCI) may result in the alteration central neurotransmitter secretion or production, which in turn may cause a hypothalamus-pituitary-adrenal axis dysfunction, leading to decreases in testosterone and other hormone levels. SCI or other acute illness or trauma characteristically includes heightened catabolism in conjunction with the lowered anabolic activity resulting in a condition that is prone to loss of lean body tissue. As long as the catabolic process goes uninterrupted, disturbed nutrient utilization will continue. The effects of the loss of lean body mass include the development of wounds and impaired healing mechanisms. Because of poor nutrition and protein combined with immobilization, patients with spinal cord injury are at high risk for bed sores.

[0025] Chronic wounds may be caused by any number of conditions, including diabetes, circulatory problems, immobilization and others. Compounding the problem, for example in diabetes, is the presence of neuropathy, which increases the risk of foot ulceration.

[0026] While there are many treatments and therapies for these conditions, none are ideal. Since the androgen receptor (AR) signaling pathway has been shown to increase lean muscle mass, muscle strength and muscle protein synthesis, and since hypogonadism accompanies these conditions, molecules targeting the AR signaling pathway may be useful in treating these diseases and/or conditions.

SUMMARY OF THE INVENTION

[0027] In one embodiment, the present invention provides a compound represented by the structure of formula S-(I):



S-(I)

[0028] In one embodiment, the present invention provides a composition comprising the compound of formula S-(I) and a pharmaceutically acceptable carrier, diluent, or salt, or a combination thereof.

[0029] The present invention also provides the compound S-(I), or the composition comprising the compound of formula S-(I) and the pharmaceutically acceptable carrier, diluent, or salt, or combination thereof, for use as a medicament.

[0030] As described herein, the compound is a selective androgen receptor modulator (SARM). In one embodiment, the SARM is a partial agonist. In one embodiment, the SARM is a tissue-selective agonist, or in some embodiments, a tissue-selective antagonist.

[0031] In one embodiment, this invention provides a composition comprising a compound represented by the structure of formula S-(I) for use in contraception in a male subject; hormone therapy; treating a subject suffering from prostate cancer; delaying the progression of prostate cancer; treating a bone-related disorder in a subject; increasing a bone mass in a subject; promoting bone formation; treating, reducing the incidence of, delaying progression of, reducing the severity of, or alleviating symptoms associated with a muscle wasting disorder; treating, reducing the severity of, reducing the incidence of, delaying the onset of, or reducing pathogenesis of diabetes, glucose intolerance, hyperinsulinemia, insulin resistance, diseases associated with diabetes, fatty liver conditions, cardiovascular disease or cachexia; treating a disease or condition of the eye; reducing a fat mass; or increasing a lean mass.

[0032] According to this aspect, and in one embodiment, the bone-related disorder is selected from osteoporosis, osteopenia, increased bone resorption, bone fracture, bone frailty, loss of bone mineral density (BMD), or any combination thereof. In one embodiment, the the composition increases the strength of a bone, stimulates or enhances osteoblastogenesis, or inhibits osteoclast proliferation.

[0033] According to this aspect, and in one embodiment, the muscle wasting disorder is due to a pathology, illness, disease or condition. In one embodiment, the pathology, illness, disease or condition is neurological, infectious, chronic or genetic. In one embodiment, the pathology, illness, disease or condition is a muscular dystrophy, a muscular atrophy, X-linked spinal-bulbar muscular atrophy (SBMA), a cachexia, malnutrition, leprosy, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), cancer, end stage renal failure, sarcopenia, emphysema, osteomalacia, HIV infection, AIDS, or cardiomyopathy.

[0034] In one embodiment, the muscle wasting disorder is an age-associated muscle wasting disorder, a disuse deconditioning-associated muscle wasting disorder, or the muscle wasting disorder is due to chronic lower back pain, burns, central nervous system (CNS) injury or damage, peripheral nerve injury or damage, spinal cord injury or damage, chemical injury or damage, or alcoholism.

[0035] In one embodiment, the disease or condition of the eye comprises Sjögren's syndrome, or xerophthalmia.

[0036] Also described herein are methods of suppressing spermatogenesis; contraception in a male; hormone therapy; treating prostate cancer; delaying the progression of prostate cancer; treating a bone-related disorder in a subject, or increasing a bone mass in a subject and/or promoting bone formation in a subject; treating, reducing the incidence of, delaying progression of, reducing the severity of, or alleviating symptoms associated with a muscle wasting disorder; treating, reducing the severity of, reducing the incidence of, delaying the onset of, or reducing pathogenesis of diabetes, glucose intolerance, hyperinsulinemia, insulin resistance, diseases associated with diabetes, fatty liver conditions, cardiovascular disease, or cachexia; treating a disease or condition of the eye; reducing a fat mass; or increasing a lean mass in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawings in which:

Figure 1: Synthetic schemes for the preparation of compound of formula (I). **Fig 1A** is a synthetic scheme for the preparation of an (S) enantiomer of a compound of formula (I) (S-(I)). **Fig 1B** is a synthetic scheme for the preparation of an (R) enantiomer of a compound of formula (I) (R-(I)). **Fig 1C** is a synthetic scheme for the preparation of an (S) enantiomer of a compound of formula (I) (S-(I)) including an oxirane intermediate. **Fig 1D** is a synthetic scheme for the preparation of an (R) enantiomer of a compound of formula (I) (R-(I)) including an oxirane intermediate. **Fig 1E** is a synthetic scheme for the preparation of an (S) enantiomer of a compound of formula (I) (S-(I)) involving B-ring addition prior to A-ring addition. **Fig 1F** is a synthetic scheme for the preparation of an (R) enantiomer of a compound of formula (I) (R-(I)) involving B-ring addition prior to A-ring addition. **Fig 1G** is a synthetic scheme for the preparation of an (S) enantiomer of a compound of formula (I) (S-(I)) using 2-tribromomethyl-[1,3]dioxolan-4-one intermediate and involving B-ring addition prior to A-ring addition. **Fig 1H** is a synthetic scheme for the preparation of an (R) enantiomer of a compound of formula (I) (R-(I)) using 2-tribromomethyl-[1,3]dioxolan-4-one intermediate and involving B-ring addition prior to A-ring addition. **Fig 1I** is a synthetic scheme for preparation of a racemic mixture of a compound of formula (I), involving oxazolidinedione intermediate and B ring addition prior to A ring. **Fig 1J** is a synthetic scheme for preparation of a racemic mixture of a compound of formula (I), involving an oxirane intermediate and A ring addition prior to B ring. **Fig 1K** is a synthetic scheme for preparation of a large scale of an (S) enantiomer of a compound of formula (I) (S-(I)). **Fig 1L** is a synthetic scheme for preparation of a large scale of an (S) enantiomer of a compound of formula (I) (S-(I)), including an oxirane intermediate.

Figure 2: Effect of S-(III) on steroid receptor transactivation (agonist mode).

Figure 3: Effect of S-(III) on steroid receptor transactivation (antagonist mode).

Figure 4: Effect of S-(II) on steroid receptor transactivation (agonist mode).

Figure 5: Effect of S-(II) on steroid receptor transactivation (antagonist mode).

Figure 6: Effect of S-(I) on steroid receptor transactivation (agonist mode).

Figure 7: Effect of S-(I) on steroid receptor transactivation (antagonist mode).

Figure 8: Anabolic and androgenic activity of compound S-(I).

DETAILED DESCRIPTION OF THE PRESENT INVENTION

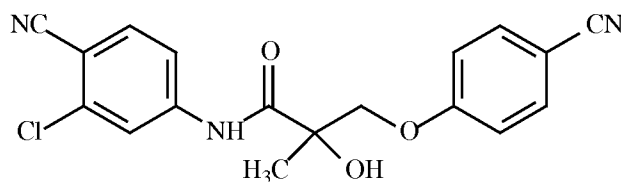
[0038] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as not to obscure the present invention.

[0039] This invention provides, in one embodiment, a substituted acylanilide characterized by the structure of Formula S-(I). In one embodiment, the compound is a SARM. In one embodiment, the compound is useful in treating a variety of conditions or diseases, including, *inter alia*, oral testosterone replacement therapy, male contraception, maintaining sexual desire in women, osteoporosis, treating prostate cancer and/or imaging prostate cancer. In some embodiments, the compounds of this invention are nonsteroidal ligands for the AR and exhibit androgenic and/or anabolic activity. In some embodiments, the compounds are partial agonists or partial antagonists in a tissue selective manner. In some embodiments, the compounds are full agonists or full antagonists in a tissue selective manner, which in some embodiments, allows for tissue-selective androgenic and/or anabolic effects. These agents may be active alone or in combination with progestins or estrogens, or other agents, as herein described. In other embodiments, the agents are agonists, antagonists, partial agonists or partial antagonists.

[0040] In some embodiments, this invention provides compounds, which are useful in androgen replacement therapy (ART), useful in a) improving body composition; b) increasing bone mineral density (BMD); c) increasing bone mass; d) increasing bone strength; e) improving bone function; f) decreasing fracture risk; g) increasing muscle strength; h) increasing muscle function; i) improving exercise tolerance; j) enhancing libido; k) improving sexual performance; l) improving mood and/or m) improving cognition.

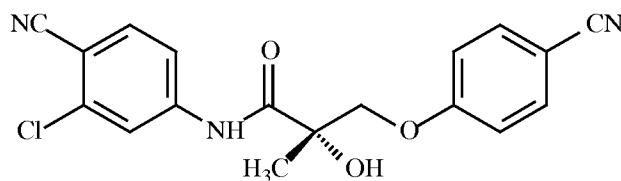
[0041] In some embodiments, described herein are synthetic processes of preparation of the SARM compounds of this invention. In some embodiments, the invention provides compositions comprising the selective androgen modulator compounds or use of the same for binding an AR, modulating spermatogenesis, bone formation and/or resorption, treating muscle wasting or diseases associated with muscle wasting, treating prostate cancer, and/or providing hormonal therapy for androgen-dependent conditions.

[0042] Described herein is a compound represented by the structure of formula (I):



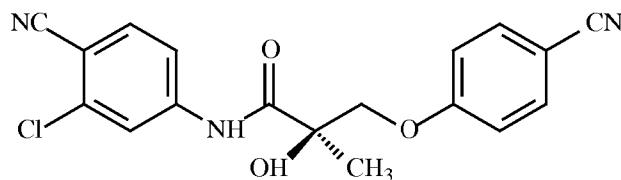
(I)

[0043] In one embodiment, the present invention provides a compound represented by the structure of formula S-(I):



S-(I)

[0044] Also described herein is a compound represented by the structure of formula R-(I):



R-(I)

[0045] The invention includes "pharmaceutically acceptable salts" of the compounds of formula S-(I) of this invention, which may be produced, by reaction of a compound of this invention with an acid or base.

[0046] Suitable pharmaceutically acceptable salts of amines of Formula S-(I) may be prepared from an inorganic acid or from an organic acid. In one embodiment, examples of inorganic salts of amines are bisulfates, borates, bromides, chlorides, hemisulfates, hydrobromates, hydrochlorates, 2-hydroxyethylsulfonates (hydroxyethanesulfonates), iodates, iodides, isothionates, nitrate, persulfates, phosphates, sulfates, sulfamates, sulfanilates, sulfonic acids (alkylsulfonates, arylsulfonates, halogen substituted alkylsulfonates, halogen substituted arylsulfonates), sulfonates and thiocyanates.

[0047] In one embodiment, examples of organic salts of amines comprise aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are acetates, arginines, aspartates, ascorbates, adipates, anthranilate, alkane carboxylates, substituted alkane carboxylates, alginates, benzenesulfonates, benzoates, bisulfates, butyrates, bicarbonates, bitartrates, carboxylate, citrates, camphorates, camphorsulfonates, cyclohexylsulfamates, cyclopentanepropionates, calcium edetates, camsylates, carbonates, clavulanates, cinnamates, dicarboxylates, digluconates, dodecylsulfonates, dihydrochlorides, decanoates, enanthuates, ethanesulfonates, edetates, edisylates, estolates, esylates, fumarates, formates, fluorides, galacturonate, gluconates, glutamates, glycolates, glucorate, glucoheptanoates, glycerophosphates, gluceptates, glycolylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxylic acids, hexylresorcinates, hydroxybenzoates, hydroxynaphthoate, hydrofluorate, lactates, lactobionates, laurates, malates, maleates, methylenebis(beta-oxynaphthoate), malonates, mandelates, mesylates, methane sulfonates, methylbromides, methylnitrates, methylsulfonates, monopotassium maleates, mucates, monocarboxylates, naphthalenesulfonates, 2-naphthalenesulfonates, nicotines, napsylates, N-methylglucamines, oxalates, octanoates, oleates, pamoates, phenylacetates, picrates, phenylbenzoates, pivalates, propionates, phthalates, phenylacetate, pectinates, phenylpropionates, palmitates, pantothenates, polygalacturates, pyruvates, quinate, salicylates, succinates, stearates, sulfanilate, subacetates, tartarates, theophyllineacetates, p-toluenesulfonates (tosylates), trifluoroacetates, terephthalates, tannates, teclates, trihaloacetates, triethiodide, tricarboxylates, undecanoates or valerates.

[0048] In one embodiment, examples of inorganic salts of carboxylic acids or phenols comprise ammonium, alkali

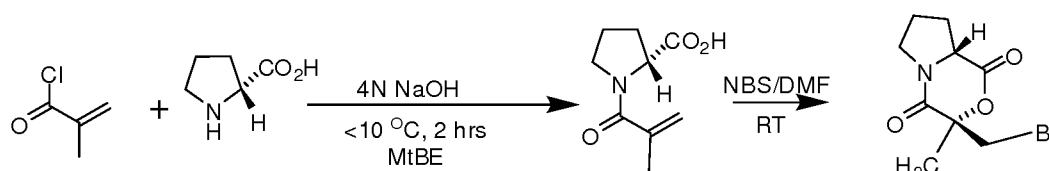
metals to include lithium, sodium, potassium, cesium; alkaline earth metals to include calcium, magnesium, aluminum; zinc, barium, chlorines or quaternary ammoniums.

[0049] In another embodiment, examples of organic salts of carboxylic acids or phenols comprise arginine, organic amines to include aliphatic organic amines, alicyclic organic amines, aromatic organic amines, benzathines, *t*-butylamines, benethamines (*N*-benzylphenethylamine), dicyclohexylamines, dimethylamines, diethanolamines, ethanolamines, ethylenediamines, hydrabamines, imidazoles, lysines, methylamines, meglamines, *N*-methyl-D-glucamines, *N,N'*-dibenzylethylenediamines, nicotinamides, organic amines, ornithines, pyridines, picolies, piperazines, procain, tris(hydroxymethyl)-methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines or ureas.

[0050] The salts may be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the ions of a existing salt for another ion or suitable ion-exchange resin.

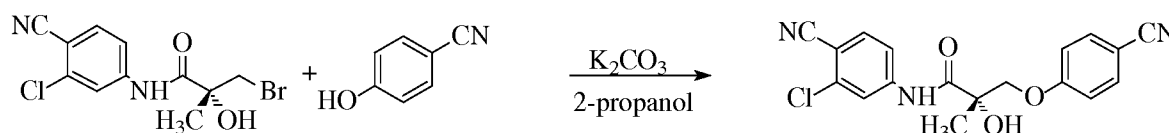
[0051] This invention provides, in other embodiments, pharmaceutical products of the compounds. The term "pharmaceutical product" refers, in other embodiments, to a composition suitable for pharmaceutical use (pharmaceutical composition), for example, as described herein.

[0052] In another embodiment, described herein is a process for the preparation of a compound of formula **S-(I)**. In one embodiment, the first step in such a process comprises that of the scheme below:

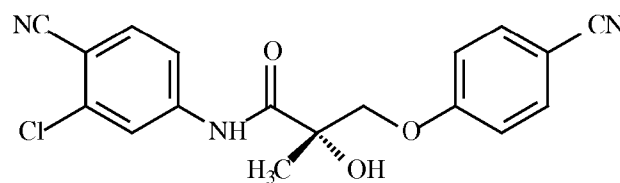
**12**

[0053] Figures 1K and 1L provide a process for the preparation of a large scale synthesis of compounds of formulas **S-(I)**.

[0054] The present application provides a process for preparing a compound represented by the structure of formula **S-(I)**, as depicted in Figure 1 and Example 1:

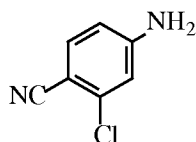
**S-(I)**

[0055] In another embodiment, described herein is a process for preparing an (*S*) enantiomer of a compound represented by the structure of formula **S-(I)**:

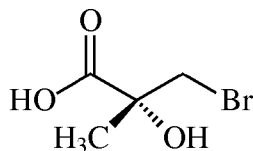
**S-(I)**

said process comprising the steps of:

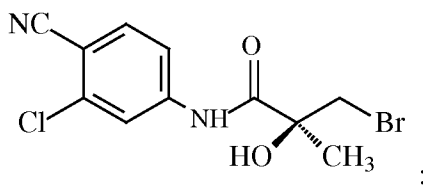
- a) coupling an amine of formula **17**:

**17**

with the carboxylic acid of formula **R-18**

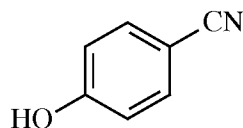
**R-18**

in the presence of a coupling reagent, to produce an amide of formula **R-19**

**R-19**

and

b) reacting the amide of formula R-19 with a compound of formula 20:

**20**

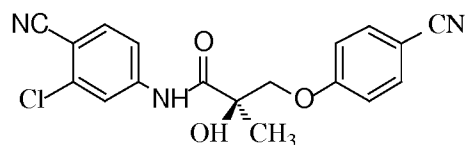
to produce a compound of formula **S-(I)**.

[0056] In one embodiment, compound **R-18** of step (a) is reacted with a coupling agent prior to addition of compound of formula **17**.

[0057] Figure 1A and Example 1 provide one embodiment of a process for the preparation of a compound of formula **S-(I)**.

[0058] In another embodiment, the conditions of step (b) of the process outlined hereinabove may comprise potassium carbonate, sodium carbonate, or cesium carbonate, or another base appropriate for this reaction, using 2-propanol, THF or methylethylketone as a solvent, optionally with a transition catalyst, BTBAC (benzyltributylammonium chloride) or other suitable agent.

[0059] In another embodiment, described herein is a process for preparing an (R) enantiomer of a compound represented by the structure of formula **R-(I)**:



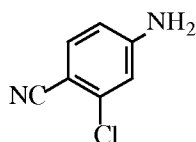
5

R-1 ;

said process comprising the steps of:

10

a) coupling an amine of formula **17**:

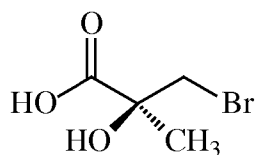


15

17

20

with the carboxylic acid of formula **S-18**

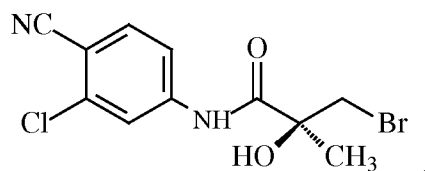


25

S-18

30

in the presence of a coupling reagent, to produce an amide of formula **S-19**



35

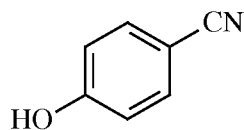
S-19 ;

40

and

45

b) reacting the amide of formula **S-19** with a compound of formula **20**



50

20

55

to produce a compound of **R-1**.

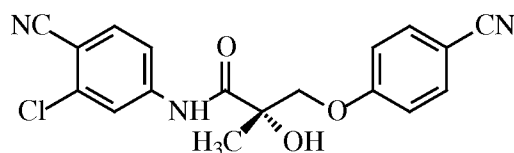
[0060] In one embodiment, compound **S-18** of step (a) is reacted with a coupling agent prior to addition of compound

of formula **17**.

[0061] Figure 1B depicts one embodiment of such a process for the preparation of compound of formula **R-(I)**.

[0062] In another embodiment, the conditions of step (b) of the process outlined hereinabove may comprise potassium carbonate, sodium carbonate, or cesium carbonate, or another base appropriate for this reaction, using 2-propanol, THF or methylethylketone as a solvent, optionally with a transition catalyst, BTBAC (benzyltributylammonium chloride) or other suitable agent.

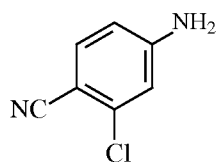
[0063] Described herein is a process for preparing an (S) enantiomer of a compound represented by the structure of formula **S-(I)**



S-(I)

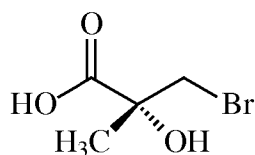
said process comprising the steps of:

a) coupling an amine of formula **17**:



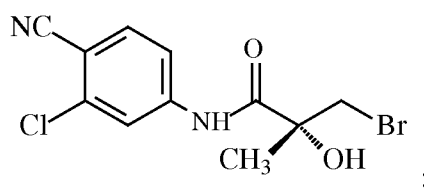
17

with the carboxylic acid of formula **R-18**



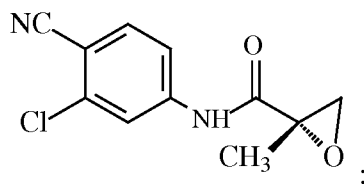
R-18

in the presence of a coupling reagent, to produce an amide of formula **R-19**



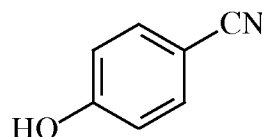
R-19

b) reacting the amide of formula **R-19**, with a base to form an oxirane **S-21**

**S-21**

10 and

c) reacting the oxirane of formula **S-21** with a compound of formula **20**:

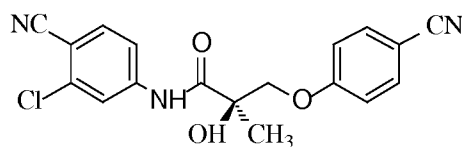
**20**

20 to produce a compound of **S-(I)**.

25 **[0064]** In one embodiment, compound **R-18** of step (a) is reacted with a coupling agent prior addition of compound of formula **17**.

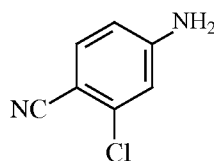
[0065] Figure 1C depicts an embodiment of such a process for the preparation of compound of formula **S-(I)**.

[0066] Also described herein is a process for preparing an (R) enantiomer of compound represented by the structure of formula **R-(I)**:

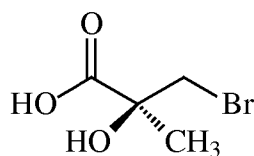
**R-(I)**

35 said process comprising the steps of:

40 a) coupling an amine of formula **17**:

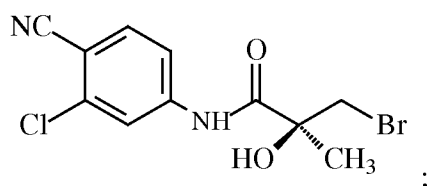


50 with the carboxylic acid of formula **S-18**

**S-18**

in the presence of a coupling reagent, to produce an amide of formula **S-19**

5

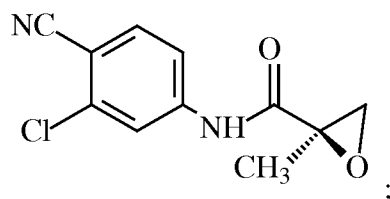


10

S-19

b) reacting the amide of formula **S-19**, with a base to form an oxirane **R-21**

15



20

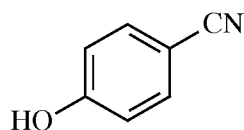
R-21

and

25

c) reacting the oxirane of formula **R-21** with a compound of formula 20;

30



20

35

to produce a compound of **R-(I)**.

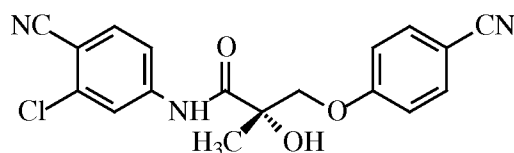
[0067] In one embodiment, compound **S-18** of step (a) is reacted with a coupling agent prior to addition of compound of formula 17.

40

[0068] Figure 1D depicts an embodiment of such a process for the preparation of compound of formula **R-(I)**.

[0069] Also described herein is a process for preparing an (S) enantiomer of a compound represented by the structure of formula **S-(I)**

45



50

S-(I)

said process comprising the steps of:

55

a) reacting a ring of formula **S-22**

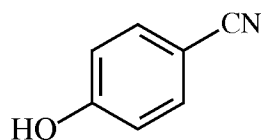
5

**S-22**

10

with a compound of **20**

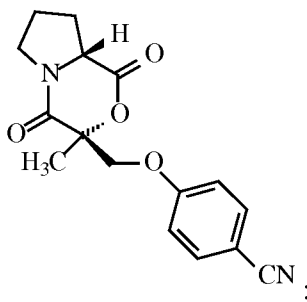
15

**20**

20

to produce a compound of formula **R-23**;

25



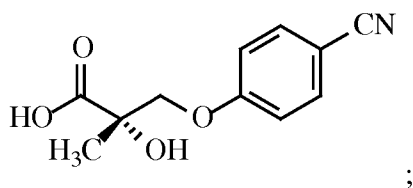
30

R-23

35

b) ring opening of compound of formula **R-23** to produce a compound of formula **S-24**

40

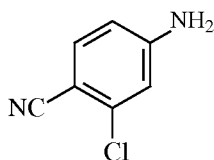
**S-24**

45

and

c) coupling the carboxylic acid of compound of formula **S-24** with the amine of formula **17**

50



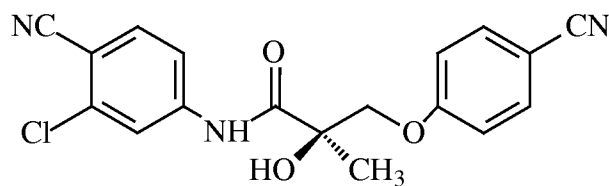
55

17to produce the compound of formula **S-(I)**

[0070] Figure 1E depicts an embodiment of such a process for the preparation of compound of formula **S-(I)**.

[0071] Further described herein is a process for preparing an (R) enantiomer of a compound represented by the structure of formula **R-(I)**:

5



10

R-(I)

said process comprising the steps of:

15

a) reacting a ring of formula **R-22**

20

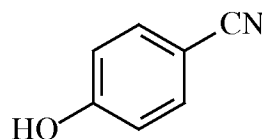


25

R-22

with a compound of **20**

30

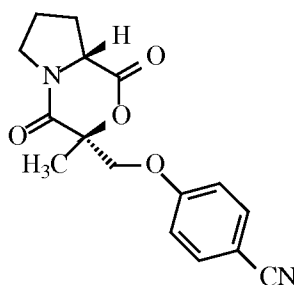


35

20

to produce a compound of formula **S-23**;

40



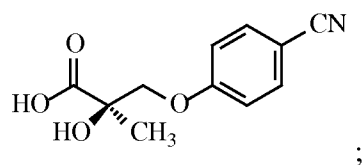
45

S-23

50

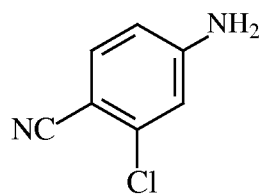
b) ring opening of compound of formula **S-23** to produce a compound of formula **R-24**:

55

**R-24**

and

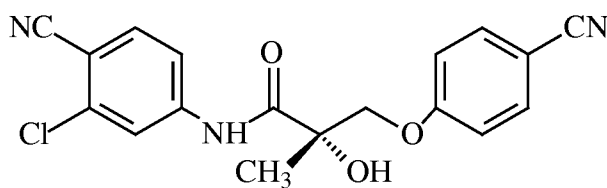
10 c) coupling the carboxylic acid of compound of formula **R-24** with the amine of formula **17**

**17**

to produce the compound of formula **R-(I)**.

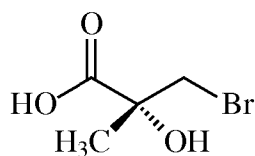
25 **[0072]** Figure 1F depicts an embodiment of such a process for the preparation of compound of formula **R-(I)**.

[0073] Described herein is a process for preparing an (*S*) enantiomer of a compound represented by the structure of formula **S-(I)**

**S-(I)**

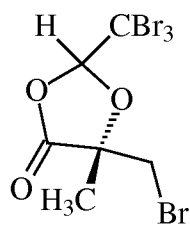
said process comprising the steps of:

40 a) reacting the carboxylic acid of formula **R-18**

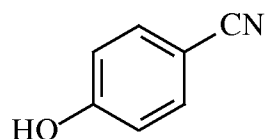
**R-18**

50 with tribromoacetaldehyde to produce a compound of formula **R-25**:

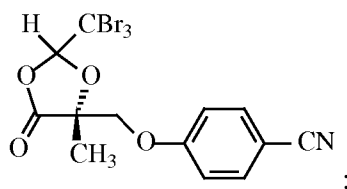
55

**R-25**

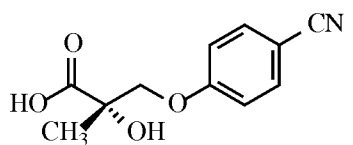
10 b) reacting the dioxalane derivative **R-25** with a compound of formula **20**

**20**

20 to produce a compound of formula **R-26**;

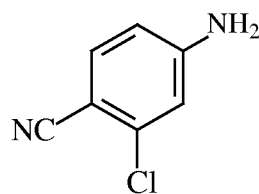
**R-26**

35 c) ring opening of compound of formula **R-26** to produce a compound of formula **S-24**

**S-24**

and

45 d) coupling the carboxylic acid of compound of formula **S-24** with the amine of formula **17**:

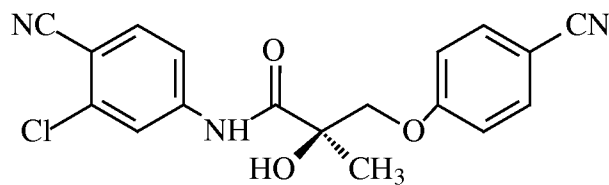
**17**

55 to produce the compound of formula **S-(I)**.

[0074] Figure 1G depicts an embodiment of such a process for the preparation of compound of formula **S-(I)**.

[0075] Also described herein is a process for preparing an (R) enantiomer of a compound represented by the structure of formula **R-(I)**

5



10

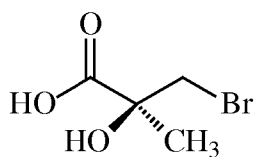
R-I

said process comprising the steps of:

15

a) reacting the carboxylic acid of formula **S-18**

20

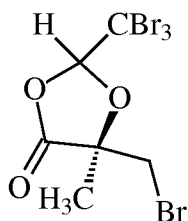


25

S-18

with tribromoacetaldehyde to produce a compound of formula **S-25**:

30



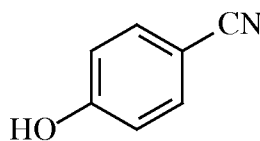
35

S-25

40

b) reacting the dioxalane derivative **S-25** with a compound of formula **20**:

45

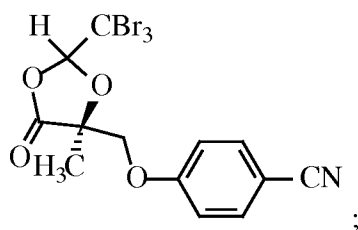


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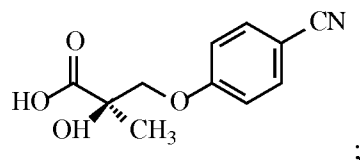
50

to produce a compound of formula **S-26**;

55

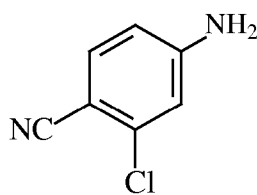
**S-26**

10 c) ring opening of compound of formula **S-26** to produce a compound of formula **R-24**

**R-24**

20 and

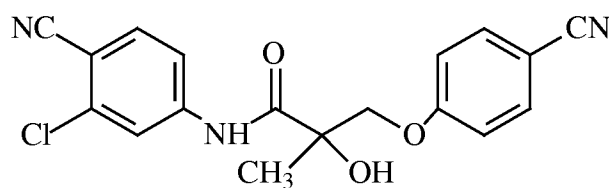
d) coupling the carboxylic acid of compound of formula **R-24** with the amine of formula **17**:

**17**

35 to produce the compound of formula **R-(I)**.

[0076] Figure 1H depicts an embodiment of such a process for the preparation of compound of formula **R-(I)**.

[0077] Still further described herein is a process for preparing a racemic mixture of a compound represented by the structure of formula **(I)**

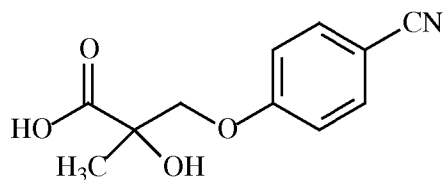
**(I)**

50 said process comprising the steps of:

a) reacting a compound of formula **24**

55

5

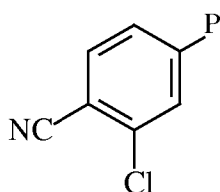


24

10

with a compound of formula 27

15

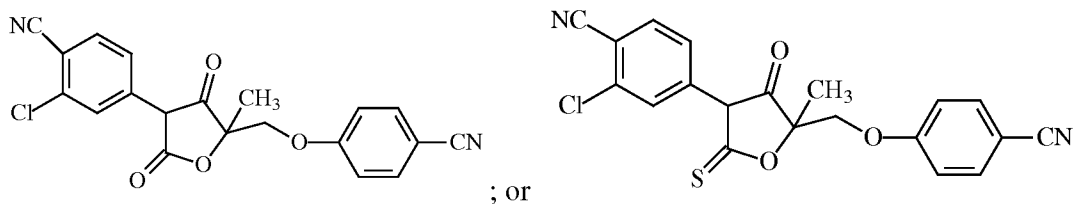


20

27

wherein P is selected from isocyanate (NCO) or isothiocyanate (NCS) to produce a compound of formula 28a or 28b, respectively

25



30

28a

28b

35

b) ring opening of the oxazolidinone or 2-thioxoxazolidinone ring of formula 28a or 28b in a presence of a base to produce a compound of formula (I).

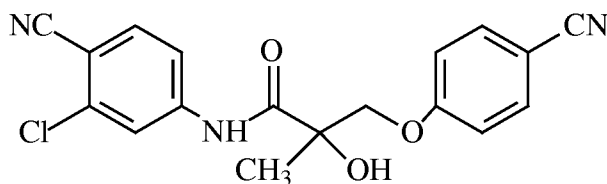
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[0078] Figure 11 depicts an embodiment of such a process for the preparation of racemic compound of formula (I).

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[0079] Also described herein is a process for preparing a racemic mixture of a compound represented by the structure of formula (I):

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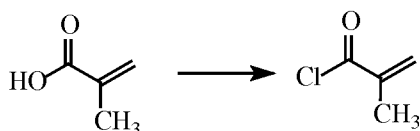
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(I)

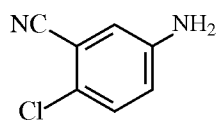
said process comprising the steps of:

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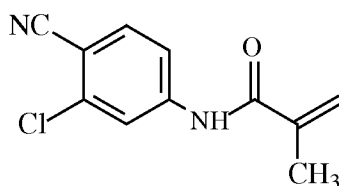
a) chlorinating methacrylic acid



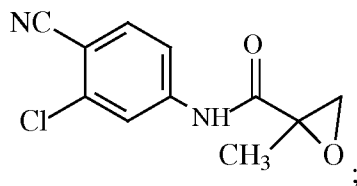
b) coupling an 3-cyano 4-trifluoromethyl aniline of formula **17** with methacryloyl chloride:

**17**

15 to produce the amide of formula **29**:

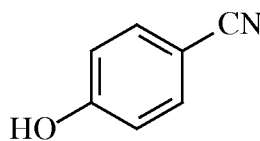
**29**

25 c) oxidizing an amide of formula **29**, to produce the oxirane of formula **21**

**21**

35 and

40 d) reacting the oxirane of formula **21** with a compound of formula **20**

**20**

50 to produce the compound of formula (I).

[0080] In another embodiment, the oxidizing an amide of formula **29** of step (c) comprises ozone. In another embodiment, the oxidizing agent is a peroxyacid, for example, peracetic acid, (CH₃COOOH). In another embodiment, the oxidizing agent is *meta*-chloroperbenzoic acid (*m*-CPBA). In another embodiment, the oxidizing agent is Magnesium MonoPeroxyPthalic Acid (MMPP). In another embodiment, the oxidizing agent is hydrogen peroxide together with catalytic amounts (1.0-0.1 mol %) of manganese (2⁺) salts.

[0081] Figure 1J depicts an embodiment of a process for the preparation of racemic compound of formula (I).

[0082] Further described herein is a process for preparing pure enantiomers of the compounds of this invention,

comprising the steps of a) preparing a racemic mixture of a compound described herein; and b) separating pure compounds of this invention from their racemic mixture.

[0083] In one embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic compounds comprises crystallization techniques. In another embodiment, the crystallization techniques include differential crystallization of enantiomers. In another embodiment, the crystallization techniques include differential crystallization of diastereomeric salts (tartaric salts or quinine salts). In another embodiment, the crystallization techniques include differential crystallization of chiral auxiliary derivatives (menthol esters, etc). In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic compounds comprises reacting the racemate mixture with another chiral group, forming of a diastereomeric mixture followed by separation of the diastereomers and removing the additional chiral group to obtain pure enantiomers. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixtures of compounds comprises chiral synthesis. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises biological resolution. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises enzymatic resolution. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises chromatographic separation using a chiral stationary phase. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises affinity chromatography. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises capillary electrophoresis. In another embodiment, separation of the optically-active (*R*) isomer or (*S*) enantiomer, from the racemic mixture of the compounds comprises forming an ester group of the hydroxyl group of the chiral carbon with an optically-active acid, for example (-)-camphoric acid, separating the diastereomers esters, thus obtained, by fractional crystallization or preferably, by flash-chromatography, and then hydrolyzing each separate ester to the alcohol.

[0084] In another embodiment, the purity, and selectivity of an enantiomer obtained by the process described herein, or by chiral separation of a racemic mixture of this invention can be determined by HPLC analysis.

[0085] In one embodiment, the reagent used for reacting the amide derivative, for example compound of formula **19** and the phenol derivative such as for example **20**, are carried out in the presence of a base. Any suitable base that will deprotonate the hydrogen of the -XH moiety (for example, a phenol moiety when X is O) and allow the coupling may be used. Nonlimiting examples of bases are carbonates such as alkali carbonates, for example sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3) and cesium carbonate (Cs_2CO_3); bicarbonates such as alkali metal bicarbonates, for example sodium bicarbonate (NaHCO_3), potassium bicarbonate (KHCO_3), alkali metal hydrides such as sodium hydride (NaH), potassium hydride (KH) and lithium hydride (LiH), and the like.

[0086] The leaving group L, according to this aspect, and in one embodiment, may comprise any removable group customarily considered for chemical reactions, as will be known to the person skilled in the art. Suitable leaving groups are halogens, for example F, Cl, Br and I; alkyl sulfonate esters (-OSO₂R) wherein R is an alkyl group, for example methanesulfonate (mesylate), trifluoromethanesulfonate, ethanesulfonate, 2,2,2-trifluoroethanesulfonate, perfluorobutanesulfonate; aryl sulfonate esters (-OSO₂Ar) wherein Ar is an aryl group, for example *p*-toluoylsulfonate (tosylate), benzenesulphonate which may be unsubstituted or substituted by methyl, chlorine, bromine, nitro and the like; NO₃, NO₂, or sulfate, sulfite, phosphate, phosphite, carboxylate, imino ester, N₂ or carbamate.

[0087] The reaction may be carried out in a suitable inert solvent or diluent such as, for example, tetrahydrofuran, diethyl ether, acetone, methyl ethyl ketone, 2-propanol, aromatic amines such as pyridine; aliphatic and aromatic hydrocarbons such as benzene, toluene, and xylene; dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAC). The reaction may be carried out in a suitable inert solvent or diluent as described hereinabove, suitably in the presence of a base such as triethylamine, and at a temperature in the range, as described above. The reaction may be carried out at an appropriate temperature, as will be known to one skilled in the art, for example, in the range, of -20 to 120 °C, or for example at or near ambient temperature.

[0088] The coupling reagent defined hereinabove is a reagent capable of turning the carboxylic acid of formula **24** or **18** into a reactive derivative thereof, thus enabling coupling with the respective amine to form an amide bond. A suitable reactive derivative of a carboxylic acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as methanol, ethanol, isopropanol, butanol or *N*-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

[0089] In one embodiment, the process for preparing a compound of this invention may involve ring opening in the presence of less acidic conditions, which may diminish the likelihood of obtaining the compound mixtures, and provide higher yield and purity of a compound of interest. In one embodiment, the ring opening of a process as described herein,

to produce a carboxylic acid of formula **18**, is carried out in the presence of HBr, which, in one embodiment, is at a concentration of up to 30 %, or in another embodiment, of up to 40 %, or in another embodiment, is of up to 25 %, or in another embodiment, of up to 23 %, or in another embodiment, of up to between 20 - 25 %. In one embodiment, the compounds of this invention may be produced via large-scale synthesis, providing highly pure products in high yields.

[0090] In one embodiment, the reaction may be carried out in a suitable inert solvent or diluent as described herein-above, suitably in the presence of a base such as triethylamine, and at a temperature in the range, as described above.

[0091] In some embodiments, the compounds as described herein are useful in preventing and treating muscle wasting disorders, bone related disorders, and diabetes related disorders.

[0092] In some embodiments, the compounds as described herein are useful, either alone or as a composition, in males and females for the treatment of a variety of hormone-related conditions, such as hypogonadism, sarcopenia, erectile dysfunction, lack of libido, osteoporosis and fertility. In some embodiments, the compounds as described herein are useful in stimulating or promoting or restoring function to various processes, which in turn result in the treatment of the conditions as herein described, including, *inter alia*, promoting erythropoiesis, osteogenesis, muscle growth, glucose uptake, insulin secretion, and/or preventing lipidogenesis, clotting, insulin resistance, atherosclerosis, osteoclast activity, and others.

[0093] In one embodiment, the use of the described compound includes contacting or binding a receptor, and thereby mediating the described effects. In some embodiments, the receptor is a nuclear receptor, which in one embodiment, is an androgen receptor, or in another embodiment, is an estrogen receptor, or in another embodiment, is a progesterone receptor, or in another embodiment, is a glucocorticoid receptor. In some embodiments, the multitude of effects may occur simultaneously, as a function of binding to multiple receptors in the subject. In some embodiments, the tissue selective effects of the compounds as described herein provide for simultaneous action on different target organs.

Pharmaceutical Compositions

[0094] In some embodiments, the uses of the present invention comprise administering a composition comprising the described compounds. As used herein, "pharmaceutical composition" means a "therapeutically effective amount" of the active ingredient, i.e. the compound of Formula S-(I), together with a pharmaceutically acceptable carrier or diluent. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen.

[0095] As used herein, the term "administering" refers to bringing a subject in contact with a compound of the present invention. As used herein, administration can be accomplished *in vitro*, i.e. in a test tube, or *in vivo*, i.e. in cells or tissues of living organisms, for example humans. In one embodiment, the present invention encompasses administering the compounds of the present invention to a subject.

[0096] The pharmaceutical compositions containing the compounds of this invention can be formulated to be administered to a subject by any route known to a person skilled in the art, such as orally, parenterally, intravascularly, paracancerally, transmucosally, transdermally, intramuscularly, intranasally, intravenously, intradermally, subcutaneously, sublingually, intraperitoneally, intraventricularly, intracranially, intravaginally, by inhalation, rectally, intratumorally, or by any means in which the recombinant virus/composition can be delivered to tissue (e.g., needle or catheter). Alternatively, topical administration may be desired for application to mucosal cells, for skin or ocular application. Another route of administration is via aspiration or aerosol formulation.

[0097] In one embodiment, the pharmaceutical compositions are to be administered orally, and are thus formulated in a form suitable for oral administration, i.e. as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets, powders, and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the SARM compounds are formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to a compound of this invention and the inert carrier or diluent, a hard gelatin capsule.

[0098] In one embodiment, the micronized capsules comprise particles containing a compound of this invention, wherein the term "micronized" used herein refers to particles having a particle size is of less than 100 microns, or in another embodiment, less than 60 microns, or in another embodiment, less than 36 microns, or in another embodiment, less than 16 microns, or in another embodiment, less than 10 microns, or in another embodiment, less than 6 microns.

[0099] Further, in another embodiment, the pharmaceutical compositions are to be administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation. Suitable liquid formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment, the pharmaceutical compositions are administered intravenously, and are thus formulated in a form suitable for intravenous administration. In another embodiment, the pharmaceutical compositions are to be administered intraarterially, and are thus formulated in a form suitable for intraarterial administration. In another embodiment, the pharmaceutical compositions are to be administered intramuscularly, and are thus formulated in a form suitable for intramuscular administration.

[0100] Further, in another embodiment, the pharmaceutical compositions are to be administered topically to body

surfaces, and are thus formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the compounds of this invention or their physiologically tolerated derivatives such as salts, esters, *N*-oxides, and the like are prepared as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

5 **[0101]** Further, in another embodiment, the pharmaceutical compositions are to be administered as a suppository, for example a rectal suppository or a urethral suppository. Further, in another embodiment, the pharmaceutical compositions are to be administered by subcutaneous implantation of a pellet. In a further embodiment, the pellet provides for controlled release of a compound as herein described over a period of time. In a further embodiment, the pharmaceutical compositions are administered intravaginally.

10 **[0102]** In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1627-1633 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 363-366 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

[0103] As used herein "pharmaceutically acceptable carriers or diluents" are well known to those skilled in the art. The carrier or diluent may be a solid carrier or diluent for solid formulations, a liquid carrier or diluent for liquid formulations, or mixtures thereof.

15 **[0104]** Solid carriers/diluents include a gum, a starch (e.g. corn starch, pregeletanized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g. microcrystalline cellulose), an acrylate (e.g. polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

[0105] In one embodiment, the compositions of this invention may include, a compound of this invention, together with one or more pharmaceutically acceptable excipients.

20 **[0106]** It is to be understood that this invention encompasses any embodiment of a compound as described herein, which in some embodiments is referred to as "a compound of this invention".

[0107] Suitable excipients and carriers may be, according to embodiments of the invention, solid or liquid and the type is generally chosen based on the type of administration being used. Liposomes may also be used to deliver the composition. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Oral dosage forms may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Parenteral and intravenous forms should also include minerals and other materials to make them compatible with the type of injection or delivery system chosen. Of course, other excipients may also be used.

25 **[0108]** For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, cyclodextrins, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil.

30 **[0109]** Parenteral vehicles (for subcutaneous, intravenous, intraarterial, or intramuscular injection) include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Examples are sterile liquids such as water and oils, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. In general, water, saline, aqueous dextrose and related sugar solutions, and glycols such as propylene glycols or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil.

35 **[0110]** In addition, the compositions may further comprise binders (e.g. acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g. cornstarch, potato starch, alginic acid, silicon dioxide, croscarmellose sodium, crospovidone, guar gum, sodium starch glycolate), buffers (e.g., Tris-HCl, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g. sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., Cremophor, glycerol, polyethylene glycerol, benzalkonium chloride, benzyl benzoate, cyclodextrins, sobitan esters, stearic acids), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g. hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g. carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g. aspartame, citric acid), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), coloring agents, lubricants (e.g. stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g. colloidal silicon dioxide), plasticizers (e.g. diethyl phthalate, triethyl citrate), emulsifiers (e.g. carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g. ethyl cellulose, acrylates, polymethacrylates), and/or adjuvants.

55 **[0111]** In one embodiment, the pharmaceutical compositions provided herein are controlled release compositions, i.e.

compositions in which the compound of this invention is released over a period of time after administration. Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another embodiment, the composition is an immediate release composition, i.e. a composition in which all of the compound is released immediately after administration.

5 **[0112]** In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. For example, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:607 (1980); Saudek et al., N. Engl. J. Med. 321:674 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 116-138 (1984). Other controlled release systems are discussed in the review by Langer (Science 249:1627-1633 (1990).

10 **[0113]** The compositions may also include incorporation of the active material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, hydrogels, etc., or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance.

15 **[0114]** Also comprehended by the invention are particulate compositions coated with polymers (e.g. poloxamers or poloxamines) and the compound coupled to antibodies directed against tissue-specific receptors, ligands or antigens or coupled to ligands of tissue-specific receptors.

20 **[0115]** Also comprehended by the invention are compounds modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline. The modified compounds are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified compounds (Abuchowski et al., 1981; Newmark et al., 1982; and Katre et al., 1987). Such modifications may also increase the compound's solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the compound, and greatly reduce the immunogenicity and reactivity of the compound. As a result, the desired *in vivo* biological activity may be achieved by the administration of such polymer-compound adducts less frequently or in lower doses than with the unmodified compound.

25 **[0116]** The preparation of pharmaceutical compositions which contain an active component is well understood in the art, for example by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the compounds of this invention or their physiologically tolerated derivatives such as salts, esters, are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions. For parenteral administration, the compounds of this invention or their physiologically tolerated derivatives such as salts, esters, *N*-oxides, and the like are converted into a solution, suspension, or emulsion, if desired with the substances customary and suitable for this purpose, for example, solubilizers or other.

30 **[0117]** An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide or antibody molecule), which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

35 **[0118]** For use in medicine, the salts of the compound will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

40 **[0119]** In one embodiment, this invention provides pharmaceutical compositions comprising a compound of this invention. In one embodiment, such compositions are useful for oral testosterone replacement therapy.

45 **[0120]** In one embodiment, this invention also provides a composition comprising two or more compounds of this invention. The present invention also relates to compositions and pharmaceutical compositions which comprise a compound of this invention alone or in combination with a progestin or estrogen, or in another embodiment, a chemotherapeutic compound, osteogenic or myogenic compound, or other agents suitable for the applications as herein described. In one embodiment, the compositions of this invention will comprise a suitable carrier, diluent or salt.

50 **[0121]** In one embodiment, the medical uses of this invention may comprise administration of a compound of formula

S-(I) of this invention at various dosages. In one embodiment, the compound of this invention is to be administered at a dosage of 0.1 - 200 mg per day. In one embodiment, the compound of this invention is to be administered at a dose of 0.1 - 10 mg, or in another embodiment, 0.1 - 26 mg, or in another embodiment, 0.1 - 60 mg, or in another embodiment, 0.3 - 16 mg, or in another embodiment, 0.3 - 30 mg, or in another embodiment, 0.6 - 26 mg, or in another embodiment, 0.6 - 60 mg, or in another embodiment, 0.76 - 16 mg, or in another embodiment, 0.76 - 60 mg, or in another embodiment, 1 - 6 mg, or in another embodiment, 1 - 20 mg, or in another embodiment, 3 - 16 mg, or in another embodiment, 30 - 60 mg, or in another embodiment, 30 - 76 mg, or in another embodiment, 100 - 2000 mg.

[0122] In one embodiment, the medical uses of this invention may comprise administration of a compound of formula S-(I) of this invention at various dosages. In one embodiment, the compound of this invention is to be administered at a dosage of 1 mg. In another embodiment the compound of this invention is to be administered at a dosage of 3 mg, 6 mg, 10 mg, 16 mg, 20 mg, 26 mg, 30 mg, 36 mg, 40 mg, 46 mg, 50 mg, 56 mg, 60 mg, 66 mg, 70 mg, 76 mg, 80 mg, 86 mg, 90 mg, 96 mg or 100 mg.

[0123] In one embodiment, the present invention provides a pharmaceutical composition comprising a) a compound as described herein; and b) a pharmaceutically acceptable carrier or diluent.

[0124] In some embodiments, the present invention provides the use of a pharmaceutical composition comprising a) any embodiment of the compounds as described herein; b) a pharmaceutically acceptable carrier or diluent; c) a flow-aid; and d) a lubricant.

[0125] In another embodiment, the present invention provides the use of a pharmaceutical composition comprising a) any embodiment of the compounds as described herein; b) lactose monohydrate; c) microcrystalline cellulose; d) magnesium stearate; and e) colloidal silicon dioxide.

[0126] In some embodiments, compositions comprising compounds of this invention offer the advantage that the compounds are nonsteroidal ligands for the androgen receptor, and exhibit anabolic activity *in vivo*. According to this aspect, such compounds are unaccompanied by serious side effects, provide convenient modes of administration, and lower production costs and are orally bioavailable, lack significant cross-reactivity with other undesired steroid receptors, and may possess long biological half-lives.

[0127] For administration to mammals, and particularly humans, it is expected that the physician will determine the actual dosage and duration of treatment, which will be most suitable for an individual and can vary with the age, weight and response of the particular individual.

[0128] In one embodiment, the compositions for administration may be sterile solutions, or in other embodiments, aqueous or non-aqueous, suspensions or emulsions. In one embodiment, the compositions may comprise propylene glycol, polyethylene glycol, injectable organic esters, for example ethyl oleate, or cyclodextrins. In another embodiment, compositions may also comprise wetting, emulsifying and/or dispersing agents. In another embodiment, the compositions may also comprise sterile water or any other sterile injectable medium.

[0129] In one embodiment, the invention provides compounds and compositions, for the medical uses of this invention, as described herein. In one embodiment, use of a compound of this invention or a composition comprising the same, will have utility in inhibiting, suppressing, enhancing or stimulating a desired response in a subject, as will be understood by one skilled in the art. In another embodiment, the compositions may further comprise additional active ingredients, whose activity is useful for the particular application for which the compound of this invention is being administered.

[0130] In some embodiments, the compositions will further comprise a 5 α -reductase inhibitors (5ARI), a SARM or SARMs, a selective estrogen receptor modulator (SERM), an aromatase inhibitor, such as but not limited to anastrozole, exemestane, or letrozole; a GnRH agonist or antagonist, a steroidal or nonsteroidal GR ligand, a steroidal or nonsteroidal PR ligand, a steroidal or nonsteroidal AR antagonist, a 17 α -aldoketoreductase inhibitor or 17 β -hydroxysteroid dehydrogenase inhibitor. Such compositions may be used for treating a hormone dependent condition, such as, for example, infertility, neoplasia of a hormone-responsive cancer, for example, a gonadal cancer, or a urogenital cancer.

[0131] In some embodiments, the composition will comprise the compounds as described herein, as well as another therapeutic compound, including *inter alia*, a 5ARI such as finasteride, dutasteride, izonsteride; other SARMs, such as, RU-58642, RU-56279, WS9761 A and B, RU-59063, RU-58841, bexlosteride, LG-2293, L-245976, LG-121071, LG-121091, LG-121104, LGD-2226, LGD-2941, YM-92088, YM-175735, LGD-1331, BMS-357597, BMS-391197, S-40503, BMS-482404, EM-4283, EM-4977, BMS-564929, BMS-391197, BMS-434588, BMS-487745, BMS-501949, SA-766, YM-92088, YM-580, LG-123303, LG-123129, PMCoI, YM-175735, BMS-591305, BMS-591309, BMS-665139, BMS-665539, CE-590, 116BG33, 154BG31, arcarine, ACP-105; SERMs, such as tamoxifene, 4-hydroxytamoxifene, idoxifene, toremifene, ospemifene, droloxifene, raloxifene, arzoxifene, bazedoxifene, PPT (1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole), DPN (diarylpropionitrile), lasofoxifene, pipendoxifene, EM-800, EM-652, nafoxidine, zindoxifene, tesmilifene, miproxifene phosphate, RU 58,688, EM 139, ICI 164,384, ICI 182,780, clomiphene, MER-25, diethylstilbestrol, coumestrol, genistein, GW5638, LY353581, zuclomiphene, enclomiphene, delmadinone acetate, DPPE, (N,N-diethyl-2-{4-(phenylmethyl)-phenoxy}ethanamine), TSE-424, WAY-070, WAY-292, WAY-818, cyclocommunol, prinaberel, ERB-041, WAY-397, WAY-244, ERB-196, WAY-169122, MF-101, ERb-002, ERB-037, ERB-017, BE-1060, BE-380, BE-381, WAY-358, [18F]FEDNP, LSN-500307, AA-102, Ban zhi lian, CT-101, CT-102, VG-101; GnRH agonists or

antagonists, such as, leuprolide, goserelin, triptorelin, alfaprostol, histrelin, detirelix, ganirelix, antide iturelix, cetorelix, ramorelix, ganirelix, antarelix, teverelix, abarelix, ozarelix, sufugolix, prazarelix, degarelix, NBI-56418, TAK-810, acyline; FSH agonist/antagonist, LH agonist/antagonists, aromatase inhibitors, such as, letrozole, anastrozole, atamestane, fadrozole, minamestane, exemestane, plomestane, liarozole, NKS-01, vorozole, YM-511, finrozole, 4-hydroxyandrostenedione, aminogluethimide, roglitimide; steroidal or nonsteroidal glucocorticoid receptor ligands, such as, ZK-216348, ZK-243149, ZK-243185, LGD-5552, mifepristone, RPR-106541, ORG-34517, GW-215864X, Sesquicillin, CP-472555, CP-394531, A-222977, AL-438, A-216054, A-276575, CP-394531, CP-409069, UGR-07; steroidal or nonsteroidal progesterone receptor ligands; steroidal or nonsteroidal AR antagonists such as flutamide, hydroxyflutamide, bicalutamide, nilutamide, hydroxysteroid dehydrogenase inhibitors, PPAR α ligand such as bezafibrate, fenofibrate, gemfibrozil; PPAR γ ligands such as darglitazone, pioglitazone, rosiglitazone, isaglitazone, rivoglitazone, netoglitazone; dual acting PPAR ligands, such as naveglitazar, farglitazar, tesaglitazar, ragaglitazar, oxeglitazar, PN-2034, PPAR δ ; 17-ketoreductase inhibitors, 3 β -DHA, 6-isomerase inhibitors, 3 β -DHT4,5-isomerase inhibitors, 17,20 desmolase inhibitors, p450c17 inhibitors, p450ssc inhibitors, 17,20-lyase inhibitors, or combinations thereof.

[0132] In some embodiments, the compositions will further comprise ghrelin receptor ligand or growth hormone analogues and secretagogues, IGF-1, IGF-1 analogues and secretagogues, myostatin analogues, proteasome inhibitors, androgenic/anabolic steroid, Enbrel, melanocortin 4 receptor agonist, insulins, or combinations thereof. Such compositions may be used for treating sarcopenia or a musculoskeletal condition.

[0133] In some embodiments, the composition will comprise the compounds as described herein, as well as another therapeutic compound, including *inter alia*, Ghrelin receptor ligand or growth hormone analogues and secretagogues, such as, pralmorelin, examorelin, tabimorelin, capimorelin, capromorelin, ipamorelin, ep-01572, ep-1572, jmv-1843; an androgenic/anabolic steroid such as testosterone/oxandrolone; a melanocortin 4 receptor agonist, such as bremelanotide; a ghrelin or analogue thereof, such as human ghrelin, CYT-009-GhrQb, L-692429, GHRP-6, SK&F-110679, U-75799E; leptin (metreleptin, pegylated leptin; a leptin receptor agonist, such as LEP(116-130), OB3, [D-Leu4]-OB3, rAAV-leptin, AAV-hOB, rAAVhOB; an insulin (short-, intermediate-, and long acting formulations); a cortisol or corticosteroid, or a combination thereof.

[0134] The invention contemplates, in some embodiments, compositions comprising the individual agents, administered separately and by similar or alternative routes, formulated as appropriately for the route of administration. The invention contemplates, in some embodiments, administration of compositions comprising the individual agents, administered in the same formulation. The invention contemplates, in some embodiments, staggered administration, concurrent administration, of administration of the various agents over a course of time, however, their effects are synergistic in the subject.

[0135] It is to be understood that any of the above means, timings, routes, or combinations thereof, of administration of two or more agents is to be considered as being encompassed by the phrase "administered in combination", as described herein.

[0136] In one embodiment, the compound of this invention is to be administered in combination with an anti-cancer agent. In one embodiment, the anti-cancer agent is a monoclonal antibody. In some embodiments, the monoclonal antibodies are used for diagnosis, monitoring, or treatment of cancer. In one embodiment, monoclonal antibodies react against specific antigens on cancer cells. In one embodiment, the monoclonal antibody acts as a cancer cell receptor antagonist. In one embodiment, monoclonal antibodies enhance the patient's immune response. In one embodiment, monoclonal antibodies act against cell growth factors, thus blocking cancer cell growth. In one embodiment, anti-cancer monoclonal antibodies are conjugated or linked to anti-cancer drugs, radioisotopes, other biologic response modifiers, other toxins, or a combination thereof. In one embodiment, anti-cancer monoclonal antibodies are conjugated or linked to a SARM compound as described hereinabove.

[0137] In another embodiment, the present invention includes compounds and compositions in which a compound of the invention is either combined with, or covalently bound to, an agent bound to a targeting agent, such as a monoclonal antibody (e.g., a murine or humanized monoclonal antibody). In one embodiment, the agent bound to a targeting agent is a cytotoxic agent. It will be appreciated that the latter combination may allow the introduction of cytotoxic agents into for example cancer cells with greater specificity. Thus, the active form of the cytotoxic agent (i.e., the free form) will be present only in cells targeted by the antibody. Of course, the compounds of the invention may also be combined with monoclonal antibodies that have therapeutic activity against cancer.

[0138] In one embodiment, the compound is administered in combination with a selective tyrosine kinase inhibitor. In some embodiments, the selective tyrosine kinase inhibitor inhibits catalytic sites of cancer promoting receptors thereby inhibiting tumor growth. In one embodiment, a selective tyrosine kinase inhibitor modulates growth factor signaling. In some embodiments, the selective tyrosine kinase inhibitor targets EGFR (ERB B/HER) family members. In one embodiment, the selective tyrosine kinase inhibitor is a BCR-ABL tyrosine kinase inhibitor. In one embodiment, the selective tyrosine kinase inhibitor is an epidermal growth factor receptor tyrosine kinase inhibitor. In one embodiment, the selective tyrosine kinase inhibitor is a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor. In one embodiment, the selective tyrosine kinase inhibitor is a Platelet Derived Growth Factor (PDGF) inhibitor.

[0139] In one embodiment, the compound is to be administered in combination with a cancer vaccine. In one embodiment, the cancer vaccine is a therapeutic vaccine thus, treating an existing cancer. In some embodiments, the cancer vaccine is a prophylactic vaccine thus, preventing the development of cancer. In one embodiment, both types of vaccines have the potential to reduce the burden of cancer. In one embodiment, treatment or therapeutic vaccines are administered to cancer patients and are designed to strengthen the body's natural defenses against cancers that have already developed. In one embodiment, therapeutic vaccines may prevent additional growth of existing cancers, prevent the recurrence of treated cancers, or eliminate cancer cells not killed by prior treatments. In some embodiments, prevention or prophylactic vaccines are administered to healthy individuals and are designed to target cancer in individuals who present high risk for the disease. In one embodiment, the cancer vaccine is an antigen/adjuvant vaccine. In one embodiment, the cancer vaccine is a whole cell tumor vaccine. In one embodiment, the cancer vaccine is a dendritic cell vaccine. In one embodiment, the cancer vaccine comprises viral vectors and/or DNA vaccines. In one embodiment, the cancer vaccine is an idiotype vaccine.

[0140] In one embodiment, the compound is to be administered in combination with an anti-cancer chemotherapeutic agent. In one embodiment, the anti-cancer chemotherapeutic agent is an alkylating agent, such as but not limited to cyclophosphamide. In one embodiment, the anti-cancer chemotherapeutic agent is a cytotoxic antibiotic such as but not limited to doxorubicin. In one embodiment, the anti-cancer chemotherapeutic agent is an antimetabolite, such as but not limited to methotrexate. In one embodiment, the anti-cancer chemotherapeutic agent is a vinca alkaloid, such as but not limited to vindesine. In some embodiments, the anti-cancer chemotherapeutic agents include platinum compounds such as but not limited to carboplatin, and taxanes such as docetaxel. In one embodiment, the anti-cancer chemotherapeutic agent is an aromatase inhibitor such as but not limited to anastrozole, exemestane, or letrozole.

[0141] In one embodiment, the compound is to be administered in combination with a Bax activity modulator such as alisol B acetate. In one embodiment, the compound is administered in combination with an angiotensin II receptor blocker such as losartan. In one embodiment, the compound is administered in combination with selenium, green tea cachecins, saw palmetto, lycopene, vitamin D, dietary soy, genistein or isoflavone.

[0142] In one embodiment, the compound is to be administered in combination with antineoplastic agents, such as alkylating agents, antibiotics, hormonal antineoplastics and antimetabolites. Examples of useful alkylating agents include alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines, such as a benzodizepa, carboquone, meturedpa and uredepa; ethylenimines and methylmelamines such as altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylol melamine; nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichine, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitroso ureas, such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol and pipobroman. More such agents will be known to those having skill in the medicinal chemistry and oncology arts.

[0143] In some embodiments, other agents suitable for combination with the compounds of this invention include protein synthesis inhibitors such as abrin, aurintricarboxylic acid, chloramphenicol, colicin E3, cycloheximide, diphtheria toxin, edeine A, emetine, erythromycin, ethionine, fluoride, 5-fluorotryptophan, fusidic acid, guanylyl methylene diphosphate and guanylyl imidodiphosphate, kanamycin, kasugamycin, kirromycin, and *O*-methyl threonine, modeccin, neomycin, norvaline, pactamycin, paromomycin, puromycin, ricin, α -sarcin, shiga toxin, showdomycin, sparsomycin, spectinomycin, streptomycin, tetracycline, thiostrepton and trimethoprim. Inhibitors of DNA synthesis, including alkylating agents such as dimethyl sulfate, mitomycin C, nitrogen and sulfur mustards, MNNG and NMS; intercalating agents such as acridine dyes, actinomycins, adriamycin, anthracenes, benzopyrene, ethidium bromide, propidium diiodide-intertwining, and agents such as distamycin and netropsin, can also be combined with compounds of the present invention in pharmaceutical compositions. DNA base analogs such as acyclovir, adenine, β -1-D-arabinoside, amethopterin, aminopterin, 2-aminopurine, aphidicolin, 8-azaguanine, azaserine, 6-azauracil, 2'-azido-2'-deoxynucleosides, 5-bromodeoxycytidine, cytosine, β -1-D-arabinoside, diazoxynorleucine, dideoxynucleosides, 5-fluorodeoxycytidine, 5-fluorodeoxyuridine, 5-fluorouracil, hydroxyurea and 6-mercaptapurine also can be used in combination therapies with the compounds of the invention. Topoisomerase inhibitors, such as coumermycin, nalidixic acid, novobiocin and oxolinic acid, inhibitors of cell division, including colcemide, colchicine, vinblastine and vincristine; and RNA synthesis inhibitors including actinomycin D, α -amanitine and other fungal amatoxins, cordycepin (3'-deoxyadenosine), dichlororibofuranosyl benzimidazole, rifampicine, streptovaricin and streptolydigin also can be combined with the compounds of the invention to provide pharmaceutical compositions.

[0144] In one embodiment, the compound is to be administered in combination with a vaccine for prostate cancer, alisol B acetate, angiotensin II receptor blocker, or others known in the art. In one embodiment, the compound is administered in combination with an agent to decrease prostate (benign or malignant) hypertrophy, such as, for example, selenium, green tea cachecins, saw palmetto, lycopene, vitamin D, dietary soy, genistein and isoflavone food product and others.

[0145] In one embodiment, the compound is to be administered in combination with an immunomodulating agent. In one embodiment, the immunomodulating agent is an immunosuppressive agent. In one embodiment, immunosuppres-

sive agents comprise corticosteroids, cyclosporine, azathioprine, methotrexate, cyclophosphamide, tacrolimus - FK-506, anti-thymocyte globulin, mycophenylate mofetil, or a combination thereof. In one embodiment, the corticosteroid is a glucocorticoid.

5 [0146] In one embodiment, the immunomodulating agent is an immunostimulatory agent. In one embodiment, the immunostimulatory agent is a specific immunostimulator thus, provides antigenic specificity during an immune response, such as a vaccine or any antigen. In one embodiment, the immunostimulatory agent is a non-specific immunostimulator thus, acting irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity. In one embodiment, the non-specific immunostimulator is Freund's complete adjuvant. In one embodiment, the non-specific immunostimulator is Freund's incomplete adjuvant. In one
10 embodiment, the non-specific immunostimulator is a montanide ISA adjuvant. In one embodiment, the non-specific immunostimulator is a Ribit's adjuvant. In one embodiment, the non-specific immunostimulator is a Hunter's TiterMax. In one embodiment, the non-specific immunostimulator is an aluminum salt adjuvant. In one embodiment, the non-specific immunostimulator is a nitrocellulose-adsorbed protein. In one embodiment, the non-specific immunostimulator is a Gerbu Adjuvant.

15 [0147] In one embodiment, the compound is to be administered in combination with an agent, which treats bone diseases, disorders or conditions, such as osteoporosis, bone fractures, etc., and this invention comprises treating the same, with the compounds as herein described, alone or in combination with other agents.

[0148] In one embodiment, bone turnover markers have been demonstrated as an effective, validated tool for the clinical scientist to monitor bone activity. In another embodiment, urinary hydroxyproline, serum alkaline phosphatase,
20 tartrate-resistant acid phosphatase, and osteocalcin levels, along with the urinary calcium-creatinine ratio are used as bone turnover markers. In another embodiment osteocalcin levels is used as a bone formation marker. In another embodiment c-telopeptide is used as a bone resorption marker.

[0149] In one embodiment, this invention provides a compound or composition for use in the treatment, prevention, suppression or inhibition of, or the reduction of the risk of developing a skeletal-related event (SRE), such as bone
25 fractures, surgery of the bone, radiation of the bone, spinal cord compression, new bone metastasis, bone loss, or a combination thereof in a subject with cancer. The invention relates, *inter alia* to treatment of an SRE with the compound of formula S-(I) in a subject with prostate cancer undergoing or having undergone androgen deprivation therapy (ADT).

[0150] In one embodiment, the skeletal-related events treated using the compositions provided herein, are fractures, which in one embodiment, are pathological fractures, non-traumatic fractures, vertebral fracture, non-vertebral fractures,
30 morphometric fractures, or a combination thereof. In some embodiments, fractures may be simple, compound, transverse, greenstick, or comminuted fractures. In one embodiment, fractures may be to any bone in the body, which in one embodiment, is a fracture in any one or more bones of the arm, wrist, hand, finger, leg, ankle, foot, toe, hip, collar bone, or a combination thereof.

[0151] In another embodiment, the compositions provided herein are effective in treatment, prevention, suppression, inhibition or reduction of the risk of skeletal-related events such as pathologic fractures, spinal cord compression, hypercalcemia, bone-related pain, or their combination.
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[0152] In another embodiment, the skeletal-related events sought to be treated using the compositions provided herein, comprise the necessity for bone surgery and/or bone radiation, which in some embodiments, is for the treatment of pain resulting in one embodiment from bone damage, or nerve compression. In another embodiment, the skeletal-related
40 events sought to be treated using the compositions provided herein, comprise spinal cord compression, or the necessity for changes in antineoplastic therapy, including changes in hormonal therapy, in a subject. In some embodiments, skeletal-related events sought to be treated using the compositions provided herein, comprise treating, suppressing, preventing, reducing the incidence of, or delaying progression or severity of bone metastases, or bone loss. In one embodiment, bone loss may comprise osteoporosis, osteopenia, or a combination thereof. In one embodiment, skeletal-related events may comprise any combination of the embodiments listed herein.

[0153] In one embodiment, the compositions provided herein are effective in reducing metastases to the bone, such as in terms of number of foci, the size of foci, or a combination thereof. According to this aspect of the invention and in one embodiment, provided herein is a composition comprising toremifene, raloxifene, tamoxifen or an analogue, functional derivative, metabolite or a combination thereof, or a pharmaceutically acceptable salt thereof for use in preventing
50 or inhibiting cancer metastasis to bone in a subject. In one embodiment, such metabolites may comprise ospemifene, fispemifene or their combination. In one embodiment, the cancer is prostate cancer.

[0154] A person skilled in the art would readily recognize that changes in the antineoplastic therapy utilizing the compositions provided herein may be conducted as a function of, or adjusted or varied as a function of, *inter alia*, the severity of the underlying disease, the source of the underlying disease, the extent of the patients' pain and source of the patients' pain, as well as the stage of the disease. The therapeutic changes may include in certain embodiments, changes in the route of administration (e.g. intracavitarily, intraarterially, intratumorally etc.), forms of the compositions administered (e.g. tablets, elixirs, suspensions etc.), changes in dosage and the like. Each of these changes is well recognized in the art and is encompassed by the embodiments provided herein.
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[0155] In one embodiment, the skeletal-related events are a result of cancer therapy. In one embodiment, the skeletal-related events are a result of hormone deprivation therapy, while in another embodiment, they are a product of androgen deprivation therapy (ADT).

[0156] In one embodiment, the compounds of this invention are useful in prevention or reversal of androgen-deprivation therapy (ADT) induced side effects such as reduced muscle mass, reduced muscle strength, frailty, hypogonadism, osteoporosis, osteopenia, decreased BMD and/or decreased bone mass.

[0157] In males, while the natural decline in sex-hormones at maturity (direct decline in androgens as well as lower levels of estrogens derived from peripheral aromatization of androgens) is associated with the frailty of bones, this effect is more pronounced in males who have undergone androgen deprivation therapy.

[0158] Such agents for combined use may comprise a SERM, as herein described, a bisphosphonate, for example, alendronate, tiludronate, clodronate, pamidronate, etidronate, alendronate, zoledronate, cimadronate, neridronate, minodronic acid, ibandronate, risedronate, homoresidronate, a calcitonin, for example, salmon, elcatonin, SUN-8577, TJN-135; a vitamin D or derivative (ZK-156979); a vitamin D receptor ligand or analogues thereof, such as calcitriol, topitriol, ZK-150123, TEI-9647, BXL-628, Ro-26-9228, BAL-2299, Ro-65-2299, DP-035; an estrogen, estrogen derivative, or conjugated estrogen; an antiestrogen, progestin, synthetic estrogen/progestin; a RANK ligand mAb, for example, denosumab or AMG162 (Amgen); an $\alpha_v\beta_3$ integrin receptor antagonist; an osteoclast vacuolar ATPase inhibitor; an antagonist of VEGF binding to osteoclast receptors; a calcium receptor antagonist; PTh (parathyroid hormone) or analogues thereof such as Forteo[®], PTHrP analogues (parathyroid hormone-related peptide), cathepsin K inhibitors (AAE581), strontium ranelate, tibolone, HCT-1026, PSK3471, gallium maltolate, Nutropin AQ[®], prostaglandins, p38 protein kinase inhibitor, a bone morphogenetic protein (BMP), an inhibitor of BMP antagonism, an HMG-CoA reductase inhibitor, a vitamin K or derivative, an antiresorptive, an ipriflavone, a fluoride salt, dietary calcium supplement, osteoprotegerin, or any combination thereof. In one embodiment, the combined administration of a SARM as herein described, osteoprotegerin and parathyroid hormone is contemplated for treating any disease, disorder or condition of the bone.

[0159] In one embodiment, the immunomodulating agent is an anti-inflammatory agent. In one embodiment, the anti-inflammatory agent is a non-steroidal anti-inflammatory agent. In one embodiment, the non-steroidal anti-inflammatory agent is a Cox-1 inhibitor. In one embodiment, the non-steroidal anti-inflammatory agent is a Cox-2 inhibitor. In one embodiment, the non-steroidal anti-inflammatory agent is a Cox-1 and Cox-2 inhibitor. In some embodiments, non-steroidal anti-inflammatory agents include aspirin, salsalate, diflunisal, ibuprofen, fenoprofen, flubiprofen, fenamate, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin, or celecoxib. In one embodiment, the anti-inflammatory agent is a steroidal anti-inflammatory agent. In one embodiment, the steroidal anti-inflammatory agent is a corticosteroid.

[0160] In one embodiment, the immunomodulating agent is an anti-rheumatic agent. In one embodiment, the anti-rheumatic agent is a non-steroidal anti-inflammatory agent. In one embodiment, the anti-rheumatic agent is a corticosteroid. In one embodiment, the corticosteroid is prednisone or dexamethasone. In one embodiment, the anti-rheumatic agent is a disease modifying anti-rheumatic drug. In one embodiment, the disease modifying anti-rheumatic drug is a slow-acting anti-rheumatic drug. In one embodiment, the disease modifying anti-rheumatic drug is an antimalarial agent. In one embodiment, disease modifying anti-rheumatic drugs include chloroquine, hydroxychloroquine, methotrexate, sulfasalazine, cyclosporine, azathioprine, cyclophosphamide, azathioprine, sulfasalazine, penicillamine, aurothioglucose, gold sodium thiomalate, or auranofin. In one embodiment, the anti-rheumatic agent is an immunosuppressive cytotoxic drug. In one embodiment, immunosuppressive cytotoxic drugs include methotrexate, mechlorethamine, cyclophosphamide, chlorambucil, or azathioprine.

[0161] In one embodiment, the compound is administered in combination with an antidiabetic agent. In one embodiment, the antidiabetic agent is a sulfonylurea. In one embodiment, sulfonylureas include tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, or gliclazide. In one embodiment, the antidiabetic agent is a meglitinide. In one embodiment, meglitinides include prandin or nateglinide. In one embodiment, the antidiabetic agent is a biguanide. In one embodiment, biguanides include metformin. In one embodiment, the antidiabetic agent is a thiazolidinedione. In one embodiment, thiazolidinediones include rosiglitazone, pioglitazone, or troglitazone. In one embodiment, the antidiabetic agent is an alpha glucosidase inhibitor. In one embodiment, alpha glucosidase inhibitors include miglitol or acarbose. In one embodiment, the antidiabetic agent is PPAR α/γ ligand, dipeptidylpeptidase 4 (DPP-4) inhibitor, SGLT (sodium-dependent glucose transporter 1) inhibitor, FBPase (fructose 1,6-bisphosphatase) inhibitor, glucagon modulators, glucocorticoid receptor (GR) antagonists, glucokinase activators (GK), glycogen phosphorylase inhibitors (GP), incretins (GLP-1 and GIP) or mimetics, beta3-adrenergic receptor agonists (β_3 -AR), carnitine palmitoyltransferase-1 (CPT-1) ligands, resistin analogs, adiponectin analogs, triacylglycerol lipases inhibitors, ciliary neurotrophic factor (CNTF) analogs, insulin-like growth factor 1 (IGF-1) or analogs, insulin receptor (IR) modulators, c-Jun N-terminal kinase (JNK) inhibitors, RXR modulators, PTP-1B phosphatase (or PTPN1) inhibitors, modulators of glycogen synthase kinase-3 (GSK3beta), 11beta-hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitors, modulators of inhibitor kappaB kinase (IKKbeta), interleukin-6 (IL-6) or TNF- α modulators.

[0162] In one embodiment, the antidiabetic agent is insulin. In one embodiment, the insulin is rapid-acting insulin. In

one embodiment, the insulin is short-acting insulin. In one embodiment, the insulin is intermediate-acting insulin. In one embodiment, the insulin is intermediate- and short-acting insulin mixtures. In one embodiment, the insulin is long-acting insulin. In one embodiment, the antidiabetic agents are inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Ser. No. 09/519,079 filed Mar. 6, 2000, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DPP4) inhibitors such as those disclosed in WO 01/68603.

[0163] In one embodiment, the compound is to be administered in combination with an agent treating the nervous system. In one embodiment, the agent treating the nervous system is an agent treating the autonomic nervous system. In one embodiment, the agent treating the autonomic nervous system is an adrenomimetic drug. In one embodiment, the adrenomimetic drug is a beta-adrenoceptor agonist, alpha-adrenoceptor agonist, or a combination thereof. In one embodiment, the adrenomimetic drug is a catecholamine. In one embodiment, adrenomimetic drugs include isoproterenol, norepinephrine, epinephrine, amphetamine, ephedrine, or dopamine. In one embodiment, the adrenomimetic drug is a directly acting adrenomimetic drug. In some embodiments, directly acting adrenomimetic drugs include phenylephrine, metaraminol, or methoxamine.

[0164] In one embodiment, the agent treating the autonomic nervous system is an adrenoceptor antagonist. In one embodiment, the adrenoceptor antagonist is a haloalkylamine, imidazoline, or quinazoline. In one embodiment, haloalkylamines include phenoxybenzamine. In one embodiment, imidazolines include phentolamine or tolazoline. In one embodiment, quinazolines include prazosin, terazosin, doxazosin, or trimazosin. In one embodiment, the adrenoceptor antagonist has a combined alpha and beta blocking activity. In one embodiment, the combined alpha and beta blocking agent is labetalol, bucindolol, carvedilol, or medroxalol.

[0165] In one embodiment, the agent treating the autonomic nervous system is a cholinomimetic agent. In one embodiment, the cholinomimetic agent is a direct-acting parasympathomimetic drug. In one embodiment, direct-acting parasympathomimetic drugs include methacholine, pilocarpine, carbachol, or bethanechol.

[0166] In one embodiment, the agent treating the autonomic nervous system is a cholinesterase inhibitor. In one embodiment, the cholinesterase inhibitor is a quaternary ammonium agent. In one embodiment, quaternary ammonium agents include edrophonium or ambenonium. In one embodiment, the cholinesterase inhibitor is a carbamate such as physostigmine, pyridostigmine, neostigmine, or rivastigmine. In one embodiment, the cholinesterase inhibitor is an organophosphate agent. In one embodiment, the inhibitor targets acetylcholine in the central nervous system such as tacrine, donepezil, or galanthamine.

[0167] In one embodiment, the agent treating the autonomic nervous system is a muscarinic blocking agent. In one embodiment, the muscarinic blocking agent is a belladonna alkaloid such as atropine or scopolamine.

[0168] In one embodiment, the agent treating the autonomic nervous system is a ganglionic blocking agent. In one embodiment, ganglionic blocking agents include nicotine, trimethaphan, or mecamylamine.

[0169] In one embodiment, the agent treating the nervous system is an agent treating the central nervous system. In one embodiment, the agent treating the central nervous system is a local anesthetic agent. In one embodiment, local anesthetic agents include benzocaine, chlorprocaine, cocaine, procaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, or ropivacaine. In one embodiment, the agent treating the central nervous system is a general anaesthetic agent. In one embodiment, general anesthetic agents include esflurane, sevoflurane, isoflurane, halothane, enflurane, methoxyflurane, xenon, propofol, etomidate, methohexital, midazolam, diazepam, ketamine, thiopentone/thiopental, or lidocaine/prilocaine.

[0170] In one embodiment, the agent treating the central nervous system is an analgesic agent. In some embodiments, analgesic agents include paracetamol or non-steroidal anti-inflammatory agent. In some embodiments, analgesic agents include opiates or morphinomimetics such as morphine, pethidine, oxycodone, hydrocodone, diamorphine, tramadol, or buprenorphine. In some embodiments, a combination of two or more analgesics is desired.

[0171] In one embodiment, the agent treating the central nervous system is a muscle relaxant or vasoconstrictor agent. In one embodiment, muscle relaxants include methocarbamol, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, orphenadrine, amyl nitrite, pancuronium, tizanidine, clonidine, or gabapentin. In one embodiment, vasoconstrictor agents include antihistamines, adrenalin dimethylarginine, caffeine, cannabis, catecholamines, decongestants, pseudoephedrine, norepinephrines, tetrahydrozoline, or thromboxane.

[0172] In one embodiment, the agent treating the central nervous system is an antiemetic drug. In one embodiment, the antiemetic drug is a 5-HT₃ receptor antagonist such as dolasetron, granisetron, ondansetron, or tropisetron. In one embodiment, the antiemetic drug is a dopamine antagonist such as domperidone, droperidol, haloperidol, chlorpromazine, promethazine, or metoclopramide. In one embodiment, the antiemetic drug is an antihistamine such as cyclizine, diphenhydramine, dimenhydrinate, or meclizine. In one embodiment, the antiemetic drug is a cannabinoid such as cannabis or marinol.

[0173] In one embodiment, the agent treating the central nervous system is a sedative agent. In one embodiment, the sedative agent is an antidepressant agent such as mirtazapine or trazodone. In one embodiment, the sedative agent is a barbiturate such as secobarbital, pentobarbital, or amobarbital. In one embodiment, the sedative agent is a benzodiazepine such as diazepam, clonazepam, alprazolam, temazepam, chlordiazepoxide, flunitrazepam, lorazepam, or

clorazepate. In one embodiment, the sedative agent is an imidazopyridines such as zolpidem or alpidem. In one embodiment, the sedative agent is a pyrazolopyrimidine such as zaleplon. In one embodiment, the sedative agent is an antihistamine such as diphenhydramine, dimenhydrinate, or doxylamine. In one embodiment, the sedative agent is an antipsychotic agent such as ziprasidone, risperidone, quetiapine, clozapine, prochlorperazine, perphenazine, loxapine, trifluoperazine, thiothixene, haloperidol, or fluphenazine. In one embodiment, the sedative agent is an herbal sedative such as valerian plant mandrake, or kava. In some embodiments, the sedative agent is eszopiclone, ramelteon, methaqualone, ethchlorvynol, chloral hydrate, meprobamate, glutethimide, methypylon, gamma-hydroxybutyrate, ethyl alcohol, methyl trichloride, zopiclone, or diethyl ether.

[0174] In one embodiment, the compound is to be administered in combination with an agent treating the cardiovascular system. In one embodiment, the agent treating the cardiovascular system is treating a congestive heart failure. In one embodiment, the agent treating congestive heart failure is an angiotensin converting enzyme (ACE) inhibitor such as benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril,trandolapril, or enalaprilat. In one embodiment, the agent treating congestive heart failure is a beta-blocker such as acebutolol, atenolol, betaxolol hydrochloride, bisoprolol fumarate, carteolol hydrochloride, carvedilol, celiprolol hydrochloride, esmolol hydrochloride, labetalol hydrochloride, levobunolol, metoprolol tartrate, metipranolol, nadolol, nebivolol, oxprenolol hydrochloride, pindolol, propranolol hydrochloride, sotalol hydrochloride, or timolol maleate. In one embodiment, the agent treating congestive heart failure is digoxin. In one embodiment, the agent treating congestive heart failure is a diuretic such as thiazide diuretic, loop diuretic, potassium-sparing diuretic, or a combination thereof. In some embodiments, thiazide diuretics include bendrofluazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclopenthiiazide, Diucardin®, Diuril®, Enduron®, Esidrix®, Exna®, HCTZ, hydrochlorothiazide, HydroDIURIL®, hydroflumethiazide, Hydromox®, Hygroton®, indapamide, Lozol®, methyclothiazide, metolazone, Mykrox®, Naqua®, Naturetin®, Oretic®, polythiazide, quinethazone, Renese®, trichlormethiazide, xipamide, or Zaroxolyn®. In some embodiments, loop diuretics include furosemide/frusemide, bumetanide, or torasemide. In some embodiments, potassium-sparing diuretics include amiloride, triamterene, aldosterone antagonists, or spironolactone.

[0175] In one embodiment, the agent treating the cardiovascular system is an anti-arrhythmic agent. In one embodiment, the anti-arrhythmic agent is a sodium channel blocker, beta-adrenergic blocker, calcium channel blocker, or an agent that prolong repolarization. In one embodiment, sodium channel blockers include quinidine, procainamide, disopyramide, lidocaine, tocainide, mexiletine, encainide, or flecainide. In one embodiment, beta-adrenergic blockers include propranolol, acebutolol, esmolol, or sotalol. In one embodiment, agents that prolong repolarization include sotalol or amiodarone. In one embodiment, calcium channel blockers include verapamil, diltiazem, nifedipine, or mebepradil. In one embodiment, the anti-arrhythmic agent is adenosine or digoxin.

[0176] In one embodiment, the agent treating the cardiovascular system is an anti-anginal agent. In one embodiment, the anti-anginal agent is an antiplatelet agent, adrenoceptor antagonist, calcium channel blocker, or a vasodilator. In some embodiments, the adrenoceptor antagonists and calcium channel blockers comprise agents as described hereinabove. In one embodiment, the antiplatelet agent is a cyclooxygenase inhibitor, ADP inhibitor, phosphodiesterase (I) inhibitor, glycoprotein IIb/IIIa inhibitor, or an adenosine reuptake inhibitor. In one embodiment, cyclooxygenase inhibitors include acetylsalicylic acid or an acetylsalicylic acid in combination with dipyridimole. In one embodiment, ADP inhibitors include clopidogrel, CS-747, or ticlopidine. In one embodiment, phosphodiesterase III inhibitors include cilostazol. In one embodiment, glycoprotein IIb/IIIa inhibitors include Abciximab, eptifibatide, integrilin, tirofiban, or aggrastat. In one embodiment, adenosine reuptake inhibitors include dipyridimole. In one embodiment, vasodilator agents include minoxidil, isosorbide dinitrate, isosorbide mononitrate, or nitroglycerine. In one embodiment, cardiac glycosides such as digitalis or ouabain may be used in combination with a SARM compound.

[0177] In one embodiment, the agent treating the cardiovascular system is a vasoactive agent or an inotrope. In one embodiment, vasoactive agents or inotropes include digoxin, dopamine, dobutamine, hydralazine, prazosin, carvedilol, nitroprusside, nitroglycerin, captopril, lisinopril, nifedipine, amlodipine, diltiazem, hydrochlorothiazide, furosemide, spironolactone, AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, arsentan and compounds disclosed in U.S. Pat. Nos. 5,612,359 and 6,043,265), dual ET/All antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), or nitrates.

[0178] In one embodiment, the agent treating the cardiovascular system is an anticoagulant agent. In one embodiment, the anticoagulant agent is a coumarin derivative or an unfractionated heparin or low molecular weight heparin. In one embodiment, coumarin derivatives include warfarin.

[0179] In one embodiment, the agent treating the cardiovascular system is a fibrinolytic agent such as streptokinase, urokinase, alteplase, anistreplase, prourokinase, reteplase, tenecteplase, lanoteplase, staphylokinase, vampire bat saliva, or alfineprase.

[0180] In one embodiment, the agent treating the cardiovascular system is a hypercholesterolemic agent such as niacin-lovastatin, colestipol HCl, fluvastatin sodium, atorvastatin calcium, simvastatin, gemfibrozil, lovastatin, pravastatin sodium, cholestyramine, cholestyramine light, fenofibrate, colessevelam HCl, or ezetimibe.

[0181] In one embodiment, the compound is to be administered in combination with an agent treating a metabolic disease, disorder or condition, which in some embodiments refers to metabolic syndrome. In some embodiments, such agents comprise, *inter alia*, pancreatic lipase inhibitors, such as for example, orlistat, cetilistat, serotonin and norepinephrine reuptake inhibitors, such as sibutramine, insulin-sensitizers such as biguanides (metformin) or PPAR agonists, dual-acting PPAR agonists (muraglitazar, tesaglitazar, naveglitazar), PPAR-delta agonists (GW-501516), DPP-IV inhibitors (vildagliptin, sitagliptin), alpha glucosidase inhibitors (acarbose), anti-diabetic combinations (ActoPlusMet, AvandaMet, metformin/pioglitazone, metformin/rosiglitazone, Glucovance, etc.), glucagon-like peptide-1 analogues (exenatide, liraglutide), amylin analogues (pramlintide), statins (atorvastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, lovastatin, pitavastatin), cholesterol absorption inhibitors (ezetimibe), nicotinic acid derivatives (immediate release and controlled release niacins, niaslo, etc.), antidyslipidemic fixed combinations (simvastatin/ezetimibe, lovastatin/nicotinic acid, atorvastatin/amlodipine, atorvastatin/torcetrapib, simvastatin/nicotinic acid (ER)), ACE inhibitors (ramipril, captopril, lisinopril), AT-II receptor antagonists (valsartan, telmisartan), cannabinoid receptor antagonists (rimonabant), cholesteryl ester transfer protein, CETP inhibitors (JTT-705, CETI-1), beta3 adrenergic agonists, PPAR α ligands, or combinations thereof.

[0182] In one embodiment, the compound is to be administered in combination with an agent treating the liver. In one embodiment, the compound is administered in combination with a statin. In some embodiment, statins include atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, or rosuvastatin.

[0183] In one embodiment, the compound is to be administered in combination with a bile acid sequestrant. In some embodiment, bile acid sequestrants include cholestyramine, colestipol, or colesevelam.

[0184] In one embodiment, the compound is to be administered in combination with a cholesterol absorption inhibitor. In some embodiment, cholesterol absorption inhibitors include ezetimibe.

[0185] In one embodiment, the compound is to be administered in combination with a nicotinic acid agent. In some embodiments, nicotinic acid agents include niacin, niacor, or sloniacin.

[0186] In one embodiment, the compound is to be administered in combination with a fibrate. In some embodiments, fibrates include gemfibrozil, or fenofibrate.

[0187] In one embodiment, the agent treating the liver is cortisone, cortisol or corticosterone. In some embodiments, the agent treating the liver is colchicine, methotrexate, ursodeoxycholic acid, or penicillamine.

[0188] In one embodiment, the compound is administered in with an agent treating the kidney. In one embodiment, the agent treating the kidney is a diuretic. In some embodiments, diuretics include organomercurial, ethacrynic acid, frusemide, humetanide, piretanide, muzolimine, chlorothiazide and thiazide, phthalimidine, chlorthalidone, clorexolone, quinazolinone, quinethazone, metolazone ilenzenesulphonamide, mefruside, chlorobenzamide, clopamidessalicylamide, xipamide, xanthine, aminophylline, carbonic anhydrase inhibitor, acetazolamide mannitol, potassium-sparing compound, aldosterone antagonist, spironolactone and canrenoate, pteridines, pyrazine, carboxamide-triamterene, or amiloride. In one embodiment, the agent treating the kidney is a steroid.

[0189] In one embodiment, the agent treating the kidney is erythropoietin. In one embodiment, erythropoietin is obtained by natural sources (e.g., urinary erythropoietin; See U.S. Pat. 3,865,801), or is a recombinantly produced protein and analogs thereof, for example, as described in U.S. Pat. Nos. 5,441,868, 5,547,933, 5,618,698 and 5,621,080 as well as human erythropoietin analogs with increased glycosylation and/or changes in the amino acid sequence as those described in European Patent Publication No. EP 668351 and the hyperglycosylated analogs having 1-14 sialic acid groups and changes in the amino acid sequence described in PCT Publication No. WO 91/05867. In one embodiment, erythropoietin-like polypeptides are administered in combination with the compounds of this invention. In some embodiments, erythropoietin-like polypeptides comprise darbepoietin (from Amgen; also known as Aranesp and novel erthyropoiesis stimulating protein (NESP)).

[0190] In one embodiment, the SARM compound is to be administered in with an agent treating a metabolic disease. In some embodiments, agents treating a metabolic disease include a vitamin, coenzyme Q10, glucosidase alfa, sodium bicarbonate, bisphosphonate, biotin, allopurinol, levodopa, diazepam, phenobarbital, haloperidol, folic acid, antioxidants, activators of cation channels haptoglobin, or carnitine.

[0191] In one embodiment, the agent treating a metabolic disease is a pancreatic lipase inhibitor such as orlistat or cetilistat, Serotonin or norepinephrine reuptake inhibitor such as sibutramine, insulin-sensitizers such as biguanide, PPAR agonist, dual-acting PPAR agonist such as muraglitazar, tesaglitazar, or naveglitazar, PPAR-delta agonist such as GW-501516, DPP-IV Inhibitor such as vildagliptin or sitagliptin, alpha glucosidase inhibitor such as acarbose, anti-diabetic combination such as ActoPlusMet, AvandaMet, metformin/pioglitazone, metformin/rosiglitazone, or Glucovance, Glucagon-like peptide-1 analogue such as exenatide or liraglutide, amylin analogue such as pramlintide, statin such as atorvastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, lovastatin, or pitavastatin, Cholesterol absorption inhibitor such as ezetimibe, Nicotinic acid derivative such as niacin or niaslo, antidyslipidemic fixed combination such as simvastatin/ezetimibe, lovastatin/nicotinic acid, atorvastatin/amlodipine, or atorvastatin/torcetrapib, simvastatin/nicotinic acid, ACE inhibitor such as ramipril, captopril, or lisinopril, AT-II receptor antagonist such as valsartan or telmisartan, cannabinoid receptor antagonist such as rimonabant, cholesteryl ester transfer protein or CETP Inhibitor such as JTT-705,

CETi-1, or beta-3 adrenergic agonist.

[0192] In one embodiment, the compound is to be administered with an agent treating a wasting disease. In some embodiments, agents treating a wasting disease include corticosteroids, anabolic steroids, cannabinoids, metoclopramide, cisapride, medroxyprogesterone acetate, megestrol acetate, cyproheptadine, hydrazine sulfate, pentoxifylline, thalidomide, anticytokine antibodies, cytokine inhibitors, eicosapentaenoic acid, indomethacin, ibuprofen, melatonin, insulin, growth hormone, clenbuterol, porcine pancreas extract, IGF-1, IGF-1 analogue and secretagogue, myostatin analogue, proteasome inhibitor, testosterone, oxandrolone, enbrel, melanocortin 4 receptor agonist, or a combination thereof.

[0193] In one embodiment, the agent treating a wasting disease is a ghrelin receptor ligand, growth hormone analogue, or a secretagogue. In some embodiments, ghrelin receptor ligands, growth hormone analogues, or secretagogues include pralmorelin, examorelin, tabimorelin, capimorelin, capromorelin, ipamorelin, EP-01572, EP-1572, or JMV-1843.

[0194] In one embodiment, growth promoting agents such as but not limited to TRH, diethylstilbestrol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Pat. No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Pat. No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Pat. No. 4,411,890 are utilized as agents treating a wasting disease.

[0195] In other embodiments, agents treating a wasting disease may comprise growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Pat. No. 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or, in other embodiments, with growth hormone releasing factor and its analogs or growth hormone and its analogs, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HTD agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. In some embodiments, agents treating a wasting disease may comprise parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate). In other embodiments, agents treating wasting disease may further comprise estrogen, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et. al., Bio. Med. Chem. Let., 9, 1003-1008 (1999) and Hamann, L. G. et. al., J. Med. Chem., 42, 210-212 (1999). In some embodiments, agents treating a wasting disease may further comprise a progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA). In some embodiments, agents treating a wasting disease may include nutritional supplements, such as those described in U.S. Pat. No. 5,179,080, which, in other embodiments are in combination with whey protein or casein, amino acids (such as leucine, branched amino acids and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D and E), minerals (e.g., selenium, magnesium, zinc, chromium, calcium and potassium), carnitine, lipoic acid, creatinine, β -hydroxy- β -methylbutyrate (Juven) and coenzyme Q. In one embodiment, agents treating a wasting disease may further comprise antire-sorptive agents, vitamin D analogues, elemental calcium and calcium supplements, cathepsin K inhibitors, MMP inhibitors, vitronectin receptor antagonists, Src SH2 antagonists, vacular-H⁺-ATPase inhibitors, ipriflavone, fluoride, tibolone, prostanoids, 17-beta hydroxysteroid dehydrogenase inhibitors and Src kinase inhibitors.

[0196] In one embodiment, the compound is to be administered in with an agent treating the endocrine system. In some embodiments, agents treating the endocrine system include radioactive iodine, antithyroid agent, thyroid hormone supplement, growth hormone, cabergoline, bromocriptine, thyroxine, gonadotropin, glucocorticoid, glucocorticoid analogue, corticotrophin, metyrapone, aminoglutethimide, mitotane, ketoconazole, mifepristone, dexamethasone somatostatin analogue, gonadotropin-releasing hormone analogue, leuprolide, goserelin, antidiuretic hormone, antidiuretic hormone analogue, oxytocin, calcium supplement, vitamin D, or a combination thereof.

[0197] In one embodiment, the agent treating the endocrine system is a 5-alpha-reductase inhibitor. In some embodiments, 5-alpha-reductase inhibitors include finasteride, dutasteride, or izonsteride.

[0198] In one embodiment, the agent treating the endocrine system is a SARM compound. In some embodiments, SARMS include RU-58642, RU-56279, WS9761 A and B, RU-59063, RU-58841, bexlosteride, LG-2293, L-245976, LG-121071, LG-121091, LG-121104, LGD-2226, LGD-2941, YM-92088, YM-175735, LGD-1331, BMS-357597, BMS-391197, S-40503, BMS-482404, EM-4283, EM-4977, BMS-564929, BMS-391197, BMS-434588, BMS-487745, BMS-501949, SA-766, YM-92088, YM-580, LG-123303, LG-123129, PMCoI, YM-175735, BMS-591305, BMS-591309, BMS-665139, BMS-665539, CE-590, 116BG33, 154BG31, arcarine, or ACP-105.

[0199] In one embodiment, the additional agent treating the endocrine system is a SERM compound. In some embodiments, SERMs include tamoxifen, 4-hydroxytamoxifene, idoxifene, toremifene, ospemifene, droloxifene, raloxifene, arzoxifene, bazedoxifene, PPT (1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole), DPN, lasofoxifene, pipendoxifene, EM-800, EM-652, nafoxidine, zindoxifene, tesmilifene, miproxifene phosphate, RU 58,688, EM 139, ICI 164,384, ICI 182,780, clomiphene, MER-25, diethylstilbestrol, coumestrol, genistein, GW5638, LY353581, zuclomiphene, enclomiphene, delmadinone acetate, DPPE, (N,N-diethyl-2-{4-(phenylmethyl)-phenoxy}ethanamine), TSE-424, WAY-070, WAY-292, WAY-818, cyclocommunol, prinaberel, ERB-041, WAY-397, WAY-244, ERB-196, WAY-169122, MF-101, ERb-002, ERB-037, ERB-017, BE-1060, BE-380, BE-381, WAY-358, [18F]FEDNP, LSN-500307, AA-102, Ban zhi lian, CT-101, CT-102, or VG-101.

[0200] In one embodiment, the agent treating the endocrine system is a gonadotropin-releasing hormone agonist or antagonist. In some embodiments, gonadotropin-releasing hormone agonists or antagonists include leuprolide, goserelin, triptorelin, alfaprostol, histrelin, detirelix, ganirelix, antide iturelix, cetorelix, ramorelix, ganirelix, antarelix, teverelix, abarelix, ozarelix, sufugolix, prazarelix, degarelix, NBI-56418, TAK-810, or acyline.

[0201] In one embodiment, the agent treating the endocrine system is a luteinizing hormone agonist or antagonist. In some embodiments, luteinizing hormone agonists or antagonists include letrozole, anastrozole, atamestane, fadrozole, minamestane, exemestane, plomestane, liarozole, NKS-01, vorozole, YM-511, finrozole, 4-hydroxyandrostenedione, aminogluethimide, or rogletimide. In one embodiment, the agent treating the endocrine system is a follicle stimulating hormone agonist or antagonist. In one embodiment, the agent treating the endocrine system is a luteinizing hormone releasing hormone (LHRH) or a LHRH analog.

[0202] In one embodiment, the agent treating the endocrine system is a steroidal or nonsteroidal glucocorticoid receptor ligand. In some embodiments, nonsteroidal glucocorticoid receptor ligands include ZK-216348, ZK-243149, ZK-243185, LGD-5552, mifepristone, RPR-106541, ORG-34517, GW-215864X, sesquicillin, CP-472555, CP-394531, A-222977, AL-438, A-216054, A-276575, CP-394531, CP-409069, or UGR-07.

[0203] In one embodiment, the agent treating the endocrine system is a steroidal or nonsteroidal progesterone receptor ligand. In one embodiment, the agent treating the endocrine system is a steroidal or nonsteroidal androgen receptor antagonist. In some embodiments, steroidal or nonsteroidal androgen receptor antagonists include flutamide, hydroxyflutamide, bicalutamide, nilutamide, or hydroxysteroid dehydrogenase inhibitor.

[0204] In one embodiment, the agent treating the endocrine system is a peroxisome proliferator-activated receptor ligand. In some embodiments, peroxisome proliferator-activated receptor ligands include bezafibrate, fenofibrate, gemfibrozil, darglitazone, pioglitazone, rosiglitazone, isaglitazone, rivoglitazone, netoglitazone, naveglitazar, farglitazar, tesaglitazar, ragaglitazar, oxeglitazar, or PN-2034.

[0205] In one embodiment, an agent treating the endocrine system is a human growth hormone. In some embodiments, human growth hormones include somatotropin or analogues.

[0206] In one embodiment, the agent treating the endocrine system is a ghrelin. In some embodiments, ghrelins include human ghrelin, CYT-009-GhrQb, L-692429, GHRP-6, SK&F-110679, or U-75799E.

[0207] In one embodiment, the agent treating the endocrine system is a leptin. In some embodiments, leptins include metreleptin or pegylated leptin. In one embodiment, an agent treating the endocrine system is a leptin receptor agonist. In some embodiments, leptin receptor agonists include LEP(116-130), OB3, [Δ -Leu4]-OB3, rAAV-leptin, AAV-hOB, or rAAVhOB.

[0208] In one embodiment, the SARM compound is to be administered with an inhibitor of an enzyme involved in the androgen biosynthetic pathway. In some embodiments, inhibitors of enzymes involved in the androgen biosynthetic pathway include 17-ketoreductase inhibitor, 3- Δ H4,6-isomerase inhibitor, 3- Δ H4,5-isomerase inhibitor, 17,20 desmolase inhibitor, p450c17 inhibitor, p450ssc inhibitor, or 17,20-lyase inhibitor.

[0209] In one embodiment, the SARM compound is to be administered with an agent treating osteoporosis. In some embodiments, osteoporosis is induced by alcohol and/or smoking. In some embodiments, agents treating osteoporosis include SERMs, calcitonin, vitamin D, vitamin D derivatives, vitamin D receptor ligand, vitamin D receptor ligand analogue, estrogen, estrogen derivative, conjugated estrogen, antiestrogen, progestin, synthetic estrogen, synthetic progestin, RANK ligand monoclonal antibody, integrin receptor antagonist, osteoclast vacuolar ATPase inhibitor, antagonist of VEGF binding to osteoclast receptors, calcium receptor antagonist, parathyroid hormone, parathyroid hormone analogue, parathyroid hormone-related peptide, cathepsin K inhibitor, strontium ranelate, tibolone, HCT-1026, PSK3471, gallium maltolate, Nutropin AQ[®], prostaglandin, p38 protein kinase inhibitor, bone morphogenetic protein (BMP), inhibitor of BMP antagonism, HMG-CoA reductase inhibitor, vitamin K, vitamin K derivative, ipriflavone, fluoride salts, dietary calcium supplement, or osteoprotegerin.

[0210] In one embodiment, the agent treating osteoporosis is a calcitonin. In some embodiments, calcitonins include salmon, elcatonin, SUN-8577, or TJN-135.

[0211] In one embodiment, the agent treating osteoporosis is a vitamin D receptor ligand or analogue. In some embodiments, vitamin D receptor ligands or analogues include calcitriol, topitriol, ZK-150123, TEI-9647, BXL-628, Ro-26-9228, BAL-2299, Ro-65-2299, or DP-035.

[0212] In one embodiment, the SARM compound is to be administered with an agent treating pharmacotherapy induced hypogonadal and/or osteopenic and/or sarcopenic state. In some embodiments, agents treating pharmacotherapy induced hypogonadal and/or osteopenic and/or sarcopenic states include opioids, narcotics, opiates, opioids, methadone, Kadian, D2 dopamine receptor antagonist, zotepine, haloperidol, amisulpride, risperidone, anti-epileptic agent, valproic acid, carbamazepine, oxcarbamazepine, chemotherapeutic agent, methotrexate, cyclophosphamide, ifosfamide, adriamycin, doxorubicin, glucocorticoids, cyclosporine, L-thyroxine, SERMs, AI, fulvestrant, gonadotropin-releasing hormone agent, androgen deprivation agent, prolactinemia-inducing agent, serotonergic antidepressant, selective serotonin reuptake inhibitor, monoamine oxidase inhibitor, tricyclic antidepressant, antihypertensive agents, methyl dopa, reserpine, clonidine, verapamil, antidopaminergic agent, anti-emetic agent, metoclopramide, H2 receptor antagonist, cimetidine,

ranitidine, estrogen, or amphetamine.

[0213] In one embodiment, the compound of this invention is to be administered with a vitamin. In some embodiments, vitamins include vitamin D, vitamin E, vitamin K, vitamin B, vitamin C, or a combination thereof.

[0214] In one embodiment, the compound of this invention is to be administered with a behavior-modulating agent. In some embodiments, behavior-modulating agents include an anti-anxiety agent, anti-psychotic agent, anti-depressant, beta-blocker, beta-2 agonist, anticholinergic bronchodilator, theophylline, aminophylline, nedocromil sodium, sodium cromoglycate, leukotriene receptor antagonist, corticosteroid, expectorant, mucolytic agent, antihistamine, pseudoephedrine, methylphenidate, amphetamine, buspirone, benzodiazepine, dextroamphetamine, tricyclic antidepressant, serotonin reuptake inhibitor, phenothiazines, benzotropine, bupropion, propranolol, lithium, venlafaxine, haloperidol, buspirone, or a neuraminidase inhibitor.

[0215] In one embodiment, the behavior-modulating agent is a benzodiazepine. In one embodiment, benzodiazepines comprise alprazolam, chlordiazepoxide, diazepam, flurazepam, lorazepam, oxazepam, temazepam, or triazolam.

[0216] In one embodiment, the behavior-modulating agent is a phenothiazine. In one embodiment, phenothiazines comprise fluphenazine, perphenazine, thioridazine, or trifluoperazine.

[0217] In one embodiment, the behavior-modulating agent is a tricyclic antidepressant or a serotonin reuptake inhibitor. In one embodiment, tricyclic antidepressants or serotonin reuptake inhibitors comprise phenothiazine, protriptyline, fluoxetine, paroxetine, or sertraline.

[0218] In one embodiment, the compound of this invention is to be administered with an agent treating a connective tissue. In some embodiments, agents treating a connective tissue include an anti-malaria agent, a cytotoxic agent, a steroid, corticosteroid, lupus medication, imuran, cytoxan, anti-rheumatic agent, corticosteroid, nifedipine, aspirin, colchicine, captopril, penicillamine, azathioprine, methotrexate, cyclophosphamide, prednisone, nicardipine, or a nonsteroidal anti-inflammatory agent.

[0219] In one embodiment, the compound of this invention is to be administered with an agent treating an ophthalmic disease. In some embodiments, agents treating an ophthalmic disease include betagan, betimol, timoptic, betoptic, betoptic, ocpress, optipranolol, xalatan, alphagan, azopt, trusopt, cosopt, pilocar, pilagan, propine, opticrom, acular, livostin, alomide, emadine, patanol, alrex, poly-pred, pred-g, dexacidin, erythromycin, maxitrol, tobradex, blephamide, FML, ocufen, voltaren, profenal, pred forte, econpred plus, eflone, flarex, inflamase forte, betadine, gramicidin, prednisolone, betaxolol, humorsol, proparacaine, betoptic, hylartin, inflamase mild, lotemax, flurbiprofen, chloramphenicol, methazolamide, timolol, ciloxan, terramycin, ciprofloxacin, miostat, triamcinolone, miconazole, tobramycin, physostigmine, gentamicin, pilocarpine, bacitracin, goniosol, polymyxin, oxytetracycline, viroptic, vexol, suprofen, celluvisc, polytrim, illotycin, ciloxan, ocuflox, brinzolamide, cefazolin, tobex, latanoprost, indocyanine, trifluridine, phenylephrine, demecarium, neomycin, tropicamide, dexamethasone, neptazane, dipivefrin, ocuflox, vidarabine, dorzolamide, ofloxacin, epinephrine, acyclovir, carbonic anhydrase inhibitor, antihistamine vitamin A, vitamin C, vitamin E, zinc, copper, atropine, or garamycin.

[0220] In one embodiment, the compound of this invention is to be administered with a gene therapy agent. In some embodiments, gene therapy agents include an antisense agent, or a replacement gene.

[0221] In some embodiments, any of the compositions of this invention will comprise a compound of formula S-(I), in any form or embodiment as described herein. In some embodiments, any of the compositions of this invention will consist of a compound of formula S-(I), in any form or embodiment as described herein. In some embodiments, of the compositions of this invention will consist essentially of a compound of S-(I), in any form or embodiment as described herein. In some embodiments, the term "comprise" refers to the inclusion of the indicated active agent, such as the compound of formula S-(I), as well as inclusion of other active agents, and pharmaceutically acceptable carriers, excipients, emollients, stabilizers, etc., as are known in the pharmaceutical industry. In some embodiments, the term "consisting essentially of" refers to a composition, whose only active ingredient is the indicated active ingredient, however, other compounds may be included which are for stabilizing, preserving, etc. the formulation, but are not involved directly in the therapeutic effect of the indicated active ingredient. In some embodiments, the term "consisting essentially of" may refer to components which facilitate the release of the active ingredient. In some embodiments, the term "consisting" refers to a composition, which contains the active ingredient and a pharmaceutically acceptable carrier or excipient.

Biological Activity of Selective Androgen Modulator Compounds

[0222] The compounds of this invention may be useful, in some embodiments, for oral testosterone replacement therapy. In other embodiments, appropriately substituted compounds are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with ADAM, such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, and alterations in mood and cognition; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer

and ovarian cancer; d) treatment and/or prevention of chronic muscular wasting; e) treatment of prostate cancer, imaging of prostate cancer; decreasing the incidence of, halting or causing a regression of prostate cancer; f) treatment of diabetes type I; g) treatment of diabetes type II; h) suppressing or inhibiting or reducing the incidence of diabetes i) treatment of glucose intolerance; j) treatment of hyperinsulinemia; k) treatment of insulin resistance 1) treatment of diabetic nephropathy; m) treatment of diabetic neuropathy; n) treatment of diabetic retinopathy; o) treatment of fatty liver condition; p) treatment of cachexia; q) oral androgen replacement and/or other clinical therapeutic and/or diagnostic areas, including any embodiment of what is encompassed by the term "treating" as described herein.

[0223] In some embodiments, the compound of this invention possesses *in vivo* tissue selective androgenic and anabolic activity, which is accordingly utilized for particular applications, as will be appreciated by one skilled in the art.

[0224] In one embodiment, the compound or composition of this invention is useful a) for treating a subject having a muscle wasting disorder; b) for treating a subject suffering from malnutrition; c) for treating a bone-related disorder in a subject; d) for increasing a bone mass in a subject; e) for improving the lipid profile in a subject; f) for treating atherosclerosis and its associated diseases; g) for improving dexterity and movement in a subject; h) for treating a subject having dwarfism; i) for treating a subject having dysmenorrhea; j) for treating a subject having dysparunia; k) for treating a subject having dysspermatogenic sterility.

[0225] In one embodiment, the compound or composition of this invention is useful in a subject, which is a human. In another embodiment, the subject is a mammal. In another embodiment the subject is an animal. In another embodiment the subject is an invertebrate. In another embodiment the subject is a vertebrate.

[0226] In one embodiment, the subject is male. In another embodiment, the subject is female. In some embodiments, while the compounds and compositions as described herein may be useful for treating either males or females, females may respond more advantageously to administration of certain compounds, for certain uses, as described and exemplified herein.

[0227] In some embodiments, while the compound or composition as described herein may be useful for treating either males or females, males may respond more advantageously to administration of certain compounds, for certain uses, as described herein.

[0228] In some embodiments, the compound as described herein and/or compositions comprising the same may be used for applications in and/or treating diseases and/or conditions associated with problems with a subject's libido, or erectile dysfunction in a subject. In one embodiment, "libido", may refer to sexual desire.

[0229] In one embodiment, the term "erectile" refers to the ability to be erect or upright. An erectile tissue is a tissue, which is capable of being greatly dilated and made rigid by the distension of the numerous blood vessels, which it contains.

[0230] In another embodiment of the present invention, a use is provided for hormonal therapy in a patient (i.e., one suffering from an androgen-dependent condition) which includes contacting an androgen receptor of a patient with a compound and/or a non steroidal agonist of the present invention in an amount effective to bind the compound to the androgen receptor and effect a change in an androgen-dependent condition.

[0231] In one embodiment of this invention, a use is provided for hormone replacement therapy in a patient (i.e., one suffering from an androgen-dependent condition) which includes administering a compound as herein described to a subject, in an amount sufficient to effect a change in a hormone-dependent condition in the subject.

[0232] Androgen-dependent conditions which may be treated with the compounds and/or compositions as herein described, include those conditions which are associated with aging, hypogonadism, sarcopenia, diminished erythropoiesis, osteoporosis, and any other conditions dependent upon low androgen (e.g., testosterone) or estrogen levels.

[0233] Androgen-dependent conditions which may be treated with the compounds and/or compositions as herein described, may comprise conditions characterized by elevated androgen or estrogen levels, including hirsutism, infertility, polycystic ovarian syndrome, endometrial carcinoma, breast cancer, male pattern baldness, prostate cancer, testicular cancer, and others, as will be known to one skilled in the art. For such conditions, the subject may be administered a compound as herein described, alone or in combination with another therapeutic agent, as will be appreciated by one skilled in the art.

[0234] In one embodiment, this invention provides a compound and compositions for use in the treatment of a cancer in a subject, reduction of incidence or severity or pathogenesis of a cancer in a subject, delaying progression, prolonging remission or delaying onset of cancer in a subject. In some embodiments, such cancers are hormone-dependent or androgen receptor dependent tumors (malignant or benign) associated with reproductive tissue in males or females, such as cancer of the prostate, ovary, breast, uterus, testicle, or others.

[0235] In some embodiments, this invention provides compounds and compositions for use in the treatment of a precancerous precursor or lesion in a subject, reduction of incidence of precancerous precursors or lesions in a subject. In some embodiments, such precancerous precursors are androgen receptor dependent tumors found in hormone-responsive tissue or are associated with reproductive tissue in males or females, such as in the prostate, ovary, breast, uterus, testicle, or others. In some embodiments, such precancerous precursors comprise any local intraepithelial neoplasia, for example, of the prostate, the cervix, etc. In some embodiments, such compounds and compositions are useful in treating neoplasia or pre-neoplasia, dysplasia or hyperplasia in a tissue, such as in reproductive tissue in males

or females.

[0236] In one embodiment, the compound and compositions are useful in treating benign prostate hyperplasia (BPH). "BPH (benign prostate hyperplasia)" is a nonmalignant enlargement of the prostate gland, and is the most common non-malignant proliferative abnormality found in any internal organ and the major cause of morbidity in the adult male. BPH occurs in over 75% of men over 50 years of age, reaching 88% prevalence by the ninth decade. BPH frequently results in a gradual squeezing of the portion of the urethra which traverses the prostate (prostatic urethra). This causes patients to experience a frequent urge to urinate because of incomplete emptying of the bladder and urgency of urination. The obstruction of urinary flow can also lead to a general lack of control over urination, including difficulty initiating urination when desired, as well as difficulty in preventing urinary flow because of the inability to empty urine from the bladder, a condition known as overflow urinary incontinence, which can lead to urinary obstruction and to urinary failure.

[0237] In some embodiments, this invention provides a compound as herein described for use in treating, reducing the severity of, reducing the incidence of, or reducing pathogenesis of cachexia and/or cachexia associated with cancer in a subject. In another embodiment, the cancer comprise adrenocortical carcinoma, anal cancer, bladder cancer, brain tumor, brain stem glioma, brain tumor, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal, pineal tumors, hypothalamic glioma, breast cancer, carcinoid tumor, carcinoma, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, extrahepatic bile duct cancer, ewings family of tumors (Pnet), extracranial germ cell tumor, eye cancer, intraocular melanoma, gallbladder cancer, gastric cancer, germ cell tumor, extragonadal, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma, laryngeal cancer, leukemia, acute lymphoblastic, leukemia, oral cavity cancer, liver cancer, lung cancer, non small cell lung cancer, small cell, lymphoma, AIDS-related lymphoma, central nervous system (primary), lymphoma, cutaneous T-cell, lymphoma, Hodgkin's disease, non-Hodgkin's disease, malignant mesothelioma, melanoma, Merkel cell carcinoma, metastatic squamous carcinoma, multiple myeloma, plasma cell neoplasms, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, osteosarcoma, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, exocrine, pancreatic cancer, islet cell carcinoma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pheochromocytoma cancer, pituitary cancer, plasma cell neoplasm, prostate cancer, rhabdomyosarcoma, rectal cancer, renal cell cancer, salivary gland cancer, Sezary syndrome, skin cancer, cutaneous T-cell lymphoma, skin cancer, Kaposi's sarcoma, skin cancer, melanoma, small intestine cancer, soft tissue sarcoma, soft tissue sarcoma, testicular cancer, thymoma, malignant, thyroid cancer, urethral cancer, uterine cancer, sarcoma, unusual cancer of childhood, vaginal cancer, vulvar cancer, Wilms' tumor, or any combination thereof.

[0238] In another embodiment, this invention provides a compound as herein described for use in treating, reducing the severity of, reducing the incidence of, delaying the onset of lung cancer.

[0239] In another embodiment, this invention provides a compound as herein described for use in treating, reducing the severity of, reducing the incidence of, delaying the onset of non small cell lung cancer.

[0240] In some embodiments, this invention provides a compound as herein described for use in treating, reducing the severity of, reducing the incidence of, or reducing pathogenesis of cancer. In another embodiment, the cancer comprises androgen AR dependent tumors (malignant or benign) such as prostate cancer, breast cancer (male or female, operable or inoperable). In another embodiment the SARM compounds adjunct to ADT for treating prostate cancer; bladder cancers; brain cancers; bone tumors, colon cancer, endometrial cancer, liver cancer, lung cancer, lymphatic cancer, kidney cancer, osteosarcoma cancer, ovarian cancer, pancreas cancer, penis cancer, skin cancer, thyroid cancer; and/or hormone-dependent cancers.

[0241] In one embodiment, this invention provides a compound as herein described for use in a) treating a bone related disorder; b) preventing a bone related disorder; c) suppressing a bone related disorder; d) inhibiting a bone related disorder; e) increasing a strength of a bone of a subject; f) increasing a bone mass in a subject; or g) inhibiting osteoclastogenesis.

[0242] In one embodiment, this invention provides a compound as herein described for use in a) accelerating bone repair; b) treating bone disorders; c) treating bone density loss; d) treating low bone mineral density (BMD); e) treating reduced bone mass; f) treating metabolic bone disease; g) promoting bone growth or regrowth; h) promoting bone restoration; i) promoting bone fracture repair; j) promoting bone remodeling; k) treating bone damage following reconstructive surgery including of the face, hip, or joints; l) enhancing of bone strength and function; m) increasing cortical bone mass; or n) increasing trabecular connectivity.

[0243] In one embodiment, the bone related disorder is a genetic disorder, or in another embodiment, is induced as a result of a treatment regimen for a given disease. For example, and in one embodiment, the compounds as herein described are useful in treating a bone-related disorder that arises as a result of cancer metastasis to bone, or in another embodiment, as a result of androgen-deprivation therapy, for example, given in response to prostate carcinogenesis in the subject.

[0244] In one embodiment, the bone-related disorder is osteoporosis. In another embodiment, the bone-related disorder is osteopenia. In another embodiment, the bone-related disorder is increased bone resorption. In another embodiment,

the bone-related disorder is bone fracture. In another embodiment, the bone-related disorder is bone frailty.

[0245] In another embodiment, the bone-related disorder is a loss of bone mineral density (BMD). In another embodiment, the bone-related disorder is any combination of osteoporosis, osteopenia, increased bone resorption, bone fracture, bone frailty and loss of BMD.

[0246] "Osteoporosis" refers, in one embodiment, to a thinning of the bones with reduction in bone mass due to depletion of calcium and bone protein. In another embodiment, osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In osteoporotic patients, bone strength is abnormal, in one embodiment, with a resulting increase in the risk of fracture. In another embodiment, osteoporosis depletes both the calcium and the protein collagen normally found in the bone, in one embodiment, resulting in either abnormal bone quality or decreased bone density. In another embodiment, bones that are affected by osteoporosis can fracture with only a minor fall or injury that normally would not cause a bone fracture. The fracture can be, in one embodiment, either in the form of cracking (as in a hip fracture) or collapsing (as in a compression fracture of the spine). The spine, hips, and wrists are common areas of osteoporosis-induced bone fractures, although fractures can also occur in other skeletal areas. Unchecked osteoporosis can lead, in another embodiment, to changes in posture, physical abnormality, and decreased mobility.

[0247] In one embodiment, the osteoporosis results from androgen deprivation. In another embodiment, the osteoporosis follows androgen deprivation. In another embodiment, the osteoporosis is primary osteoporosis. In another embodiment, the osteoporosis is secondary osteoporosis. In another embodiment, the osteoporosis is postmenopausal osteoporosis. In another embodiment, the osteoporosis is juvenile osteoporosis. In another embodiment, the osteoporosis is idiopathic osteoporosis. In another embodiment, the osteoporosis is senile osteoporosis.

[0248] In another embodiment, the primary osteoporosis is type I primary osteoporosis. In another embodiment, the primary osteoporosis is type II primary osteoporosis.

[0249] According to this aspect of the invention and in one embodiment, the bone-related disorder is treated with a compound as herein described, or a combination thereof. In another embodiment, other bone-stimulating compounds can be provided to the subject, prior to, concurrent with or following administration of a compound or compounds as herein described. In one embodiment, such a bone stimulating compound may comprise natural or synthetic materials.

[0250] In one embodiment, the bone stimulating compound may comprise a bone morphogenetic protein (BMP), a growth factor, such as epidermal growth factor (EGF), a fibroblast growth factor (FGF), a transforming growth factor (TGF), an insulin growth factor (IGF), a platelet-derived growth factor (PDGF) hedgehog proteins such as *sonic*, *indian* and *desert* hedgehog, a hormone such as follicle stimulating hormone, parathyroid hormone, parathyroid hormone related peptide, activins, inhibins, follistatin, *frizzled*, *frzb* or *frazzled* proteins, BMP binding proteins such as chordin and fetuin, a cytokine such as IL-3, IL-7, GM-CSF, a chemokine, such as eotaxin, a collagen, osteocalcin, osteonectin and others, as will be appreciated by one skilled in the art.

[0251] In another embodiment, the compositions for use in treating a bone disorder of this invention may comprise a compound or compounds as herein described, an additional bone stimulating compound, or compounds, and osteogenic cells. In one embodiment, an osteogenic cell may be a stem cell or progenitor cell, which may be induced to differentiate into an osteoblast. In another embodiment, the cell may be an osteoblast. In another embodiment, nucleic acids which encode bone-stimulating compounds may be administered to the subject.

[0252] In one embodiment, the compound and compositions of the present invention are for use in treating osteoporosis. In another embodiment, the compound and compositions of this invention may be administered in combination with SERMs for treating osteoporosis. In another embodiment, the SERMs are tamoxifen, 4-hydroxytamoxifene, idoxifene, toremifene, ospemifene, droloxifene, raloxifene, arzoxifene, bazedoxifene, PPT (1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole), DPN, lasofoxifene, pipendoxifene, EM-800, EM-652, nafoxidine, zindoxifene, tesmillifene, miproxifene phosphate, RU 58,688, EM 139, ICI 164,384, ICI 182,780, clomiphene, MER-25, diethylstilbestrol, coumestrol, genistein, GW5638, LY353581, zuclomiphene, enclomiphene, delmadinone acetate, DPPE, (*N,N*-diethyl-2-{4-(phenylmethyl)-phenoxy}ethanamine), TSE-424, WAY-070, WAY-292, WAY-818, cyclocommunol, prinaberel, ERB-041, WAY-397, WAY-244, ERB-196, WAY-169122, MF-101, ERb-002, ERB-037, ERB-017, BE-1060, BE-380, BE-381, WAY-358, [18F]FED-NP, LSN-500307, AA-102, Ban zhi lian, CT-101, CT-102, or VG-101.

[0253] In another embodiment, the compound and compositions of the present invention may be administered in combination with bisphosphonates such as alendronate, tiludroate, clodronate, pamidronate, etidronate, alendronate, zolendronate, cimadronate, neridronate, minodronic acid, ibandronate, risedronate, or homoresidronate for treating osteoporosis.

[0254] In another embodiment, the compound and compositions of the present invention may be administered in combination with calcitonin such as salmon, Elcatonin, SUN-8577 or TJN-135 for treating osteoporosis.

[0255] In another embodiment, the compound and compositions for use in treating osteoporosis may be administered in combination with a) vitamin D or derivative such as ZK-156979; b) vitamin D receptor ligand and analogues such as calcitriol, topitriol, ZK-150123, TEI-9647, BXL-628, Ro-26-9228, BAL-2299, Ro-65-2299 or DP-035; c) estrogen, estrogen derivative, or conjugated estrogens; d) antiestrogen, progestins, or synthetic estrogen/progestins; e) RANK ligand mAb

such as denosumab formerly AMG162 (Amgen); f) $\alpha_v\beta_3$ integrin receptor antagonist; g) osteoclast vacuolar ATPase inhibitor; h) antagonist of VEGF binding to osteoclast receptors; i) calcium receptor antagonist; j) PTH (parathyroid hormone) and analogues, PTHrP analogues (parathyroid hormone-related peptide); k) cathepsin K inhibitors (AAE581, etc.); l) strontium ranelate; m) tibolone; n) HCT-1026, PSK3471; o) gallium maltolate; p) Nutropin AQ; q) prostaglandins (for osteo); r) p38 protein kinase inhibitor; s) bone morphogenetic protein; t) inhibitor of BMP antagonism; u) HMG-CoA reductase inhibitor; v) vitamin K or derivative; w) ipriflavone; x) fluoride salts; y) dietary calcium supplement, and z) osteoprotegerin.

[0256] In one embodiment, the compound or composition of this invention is useful in treating diseases or disorders caused by, or associated with a hormonal disorder, disruption or imbalance. In one embodiment, the hormonal disorder, disruption or imbalance comprises an excess of a hormone. In another embodiment, the hormonal disorder, disruption or imbalance comprises a deficiency of a hormone. In one embodiment, the hormone is a steroid hormone. In another embodiment, the hormone is an estrogen. In another embodiment, the hormone is an androgen. In another embodiment, the hormone is a glucocorticoid. In another embodiment, the hormone is a corticosteroid. In another embodiment, the hormone is luteinizing hormone (LH). In another embodiment, the hormone is follicle stimulating hormone (FSH). In another embodiment, the hormone is any other hormone known in the art. In another embodiment, the hormonal disorder, disruption or imbalance is associated with menopause. In another embodiment, the hormonal disorder, disruption or imbalance is associated with andropause, andropausal vasomotor symptoms, andropausal gynecomastia, decreased muscle strength and/or function, decreased bone strength and/or function and anger. In another embodiment, hormone deficiency is a result of specific manipulation, as a byproduct of treating a disease or disorder in the subject. For example, the hormone deficiency may be a result of androgen depletion in a subject, as a therapy for prostate cancer in the subject.

[0257] In another embodiment the invention is directed to compositions for use in treating sarcopenia or cachexia, and associated conditions related thereto, for example diseases or disorders of the bone.

[0258] In one embodiment, this invention provides a compound as herein described for use in 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder; and/or treating, preventing, inhibiting, reducing or suppressing muscle wasting due to end stage renal disease or CKD; and/or 6) treating, preventing, inhibiting, reducing or suppressing frailty.

[0259] In another embodiment, a compound of the invention for use in treating a subject having a muscle wasting disorder, or any of the disorders described herein, may be administered as a pharmaceutical composition including a compound as herein described. In another embodiment, the composition is to be administered intravenously, intraarterially, by or intramuscularly injecting to said subject said pharmaceutical composition in liquid form; subcutaneously implanting in said subject a pellet containing said pharmaceutical composition; orally administering to said subject said pharmaceutical composition in a liquid or solid form; or topically applying to the skin surface of said subject said pharmaceutical composition.

[0260] A muscle is a tissue of the body that primarily functions as a source of power. There are three types of muscles in the body: a) skeletal muscle - the muscle responsible for moving extremities and external areas of the bodies; b) cardiac muscle - the heart muscle; and c) smooth muscle - the muscle that is in the walls of arteries and bowel.

[0261] A wasting condition or disorder is defined herein as a condition or disorder that is characterized, at least in part, by an abnormal, progressive loss of body, organ or tissue mass. A wasting condition can occur as a result of a pathology such as, for example, cancer, or an infection, or it can be due to a physiologic or metabolic state, such as disuse deconditioning that can occur, for example, due to prolonged bed rest or when a limb is immobilized, such as in a cast. A wasting condition can also be age associated. The loss of body mass that occurs during a wasting condition can be characterized by a loss of total body weight, or a loss of organ weight such as a loss of bone or muscle mass due to a decrease in tissue protein.

[0262] In one embodiment, "muscle wasting" or "muscular wasting", used herein interchangeably, refer to the progressive loss of muscle mass and/or to the progressive weakening and degeneration of muscles, including the skeletal or voluntary muscles which control movement, cardiac muscles which control the heart, and smooth muscles. In one embodiment, the muscle wasting condition or disorder is a chronic muscle wasting condition or disorder. "Chronic muscle wasting" is defined herein as the chronic (i.e. persisting over a long period of time) progressive loss of muscle mass and/or to the chronic progressive weakening and degeneration of muscle.

[0263] The loss of muscle mass that occurs during muscle wasting can be characterized by a muscle protein breakdown or degradation, by muscle protein catabolism. Protein catabolism occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Protein catabolism or depletion, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting. The term "catabolism" has its commonly known meaning in the art, specifically an energy burning form of metabolism.

[0264] Muscle wasting can occur as a result of a pathology, disease, condition or disorder. In one embodiment, the

pathology, illness, disease or condition is chronic. In another embodiment, the pathology, illness, disease or condition is genetic. In another embodiment, the pathology, illness, disease or condition is neurological. In another embodiment, the pathology, illness, disease or condition is infectious. As described herein, the pathologies, diseases, conditions or disorders for which the compounds and compositions of the present invention are administered are those that directly or indirectly produce a wasting (i.e. loss) of muscle mass, that is a muscle wasting disorder.

[0265] In one embodiment, muscle wasting in a subject is a result of the subject having a muscular dystrophy; muscle atrophy; X-linked spinal-bulbar muscular atrophy (SBMA).

[0266] The muscular dystrophies are genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles that control movement. The muscles of the heart and some other involuntary muscles are also affected in some forms of muscular dystrophy. The major forms of muscular dystrophy (MD) are: Duchenne muscular dystrophy, myotonic dystrophy, Becker muscular dystrophy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy and Emery-Dreifuss muscular dystrophy.

[0267] Muscular dystrophy can affect people of all ages. Although some forms first become apparent in infancy or childhood, others may not appear until middle age or later. Duchenne MD is the most common form, typically affecting children. Myotonic dystrophy is the most common of these diseases in adults.

[0268] Muscle atrophy (MA) is characterized by wasting away or diminution of muscle and a decrease in muscle mass. For example, Post-Polio MA is a muscle wasting that occurs as part of the post-polio syndrome (PPS). The atrophy includes weakness, muscle fatigue, and pain.

[0269] Another type of MA is X-linked spinal-bulbar muscular atrophy (SBMA - also known as Kennedy's Disease). This disease arises from a defect in the androgen receptor gene on the X chromosome, affects only males, and its onset is in adulthood. Because the primary disease cause is an androgen receptor mutation, androgen replacement is not a current therapeutic strategy. There are some investigational studies where exogenous testosterone propionate is being given to boost the levels of androgen with hopes of overcoming androgen insensitivity and perhaps provide an anabolic effect. Still, use of supraphysiological levels of testosterone for supplementation will have limitations and other potentially serious complications.

[0270] Sarcopenia is a debilitating disease that afflicts the elderly and chronically ill patients and is characterized by loss of muscle mass and function. Further, increased lean body mass is associated with decreased morbidity and mortality for certain muscle-wasting disorders. In addition, other circumstances and conditions are linked to, and can cause muscle wasting disorders. For example, studies have shown that in severe cases of chronic lower back pain, there is paraspinal muscle wasting.

[0271] Muscle wasting and other tissue wasting is also associated with advanced age. It is believed that general weakness in old age is due to muscle wasting. As the body ages, an increasing proportion of skeletal muscle is replaced by fibrous tissue. The result is a significant reduction in muscle power, performance and endurance.

[0272] Long term hospitalization due to illness or injury, or disuse deconditioning that occurs, for example, when a limb is immobilized, can also lead to muscle wasting, or wasting of other tissue. Studies have shown that in patients suffering injuries, chronic illnesses, burns, trauma or cancer, who are hospitalized for long periods of time, there is a long-lasting unilateral muscle wasting, and a decrease in body mass.

[0273] Injuries or damage to the central nervous system (CNS) are also associated with muscle wasting and other wasting disorders. Injuries or damage to the CNS can be, for example, caused by diseases, trauma or chemicals. Examples are central nerve injury or damage, peripheral nerve injury or damage and spinal cord injury or damage. In one embodiment CNS damage or injury comprise Alzheimer's diseases (AD); anger (mood); anorexia, anorexia nervosa, anorexia associated with aging and/or assertiveness (mood).

[0274] In another embodiment, muscle wasting or other tissue wasting may be a result of alcoholism, and may be treated with the compounds and compositions of the invention, representing embodiments thereof.

[0275] In one embodiment, the invention provides a SARM compound as described herein for use in the treatment of a wasting disease, disorder or condition in a subject.

[0276] In one embodiment, the wasting disease, disorder or condition being treated is associated with chronic illness

[0277] This invention is directed to a compound for treating, in some embodiments, any wasting disorder, which may be reflected in muscle wasting, weight loss, malnutrition, starvation, or any wasting or loss of functioning due to a loss of tissue mass.

[0278] In some embodiments, wasting diseases or disorders, such as cachexia; malnutrition, tuberculosis, leprosy, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), cancer, end stage renal failure, sarcopenia, emphysema, osteomalacia, or cardiomyopathy, may be treated by this invention, via the administration of a SARM compound as herein described, compositions comprising the same, with or without additional drugs, compounds, or agents, which provide a therapeutic effect for the condition being treated.

[0279] In some embodiments, wasting is due to infection with enterovirus, Epstein-Barr virus, herpes zoster, HIV, trypanosomes, influenza, coxsackie, rickettsia, trichinella, schistosoma or mycobacteria, and this invention, in some

embodiments, provides treatment thereof.

[0280] Cachexia is weakness and a loss of weight caused by a disease or as a side effect of illness. Cardiac cachexia, i.e. a muscle protein wasting of both the cardiac and skeletal muscle, is a characteristic of congestive heart failure. Cancer cachexia is a syndrome that occurs in patients with solid tumors and hematological malignancies and is manifested by weight loss with massive depletion of both adipose tissue and lean muscle mass.

[0281] Cachexia is also seen in acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV)-associated myopathy and/or muscle weakness/wasting is a relatively common clinical manifestation of AIDS. Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle weakness, tenderness, and muscle atrophy.

[0282] In one embodiment, the invention comprises the use of a composition comprising a compound and an anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the central nervous system, an agent treating the gastrointestinal system, an anti-infective agent, an agent treating a metabolic disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, gastrointestinal diseases comprise adenomatous polyposis coli, Alagille syndrome, anus diseases, appendicitis, barrett esophagus, biliary atresia, biliary tract diseases, Caroli disease, celiac disease, cholangitis, cholecystitis, cholelithiasis, colitis, ulcerative, Crohn's disease, deglutition disorders, duodenal ulcer, dysentery, enterocolitis, pseudomembranous, esophageal achalasia, esophageal atresia, esophagitis, exocrine pancreatic insufficiency, fatty liver, fecal incontinence, gastritis, gastritis, hypertrophic, gastroenteritis, gastroesophageal reflux, gastroparesis, hemorrhoids, hepatic vein thrombosis, hepatitis, hepatitis, chronic, hernia, diaphragmatic, hernia, hiatal, Hirschsprung disease, hypertension (HTN), portal, inflammatory bowel diseases, intestinal diseases, intestinal neoplasms, intestinal neuronal dysplasia, intestinal obstruction, irritable bowel syndrome, lactose intolerance, liver cirrhosis, liver diseases, meckel diverticulum, pancreatic diseases, pancreatic neoplasms, pancreatitis, peptic ulcer, Peutz-Jeghers syndrome, proctitis, rectal diseases, rectal prolapse, short bowel syndrome, tracheoesophageal fistula, whipple disease, or Zollinger-Ellison syndrome.

[0283] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a respiratory tract disease in a subject. In one embodiment, the use comprises a composition comprising a compound and an anti-cancer agent, an immunomodulating agent, an agent treating the central nervous system, an agent treating the cardiovascular system, an anti-infective agent, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, respiratory tract diseases comprise airway obstruction, apnea, asbestosis, asthma, asthma-induced muscle weakness or bone weakness, atelectasis, berylliosis, bronchial diseases, bronchiectasis, bronchiolitis, bronchiolitis obliterans organizing pneumonia, bronchitis, bronchopulmonary dysplasia, chronic obstructive pulmonary disease (COPD), common cold, cough, empyema, pleural, epiglottitis, glucocorticoid (GC)-induced myopathy or osteopenia hemoptysis, hypertension, pulmonary, hyper-ventilation, kartagener syndrome, lung abscess, lung diseases, meconium aspiration syndrome, pleural effusion, pleurisy, pneumonia, pneumothorax, pulmonary alveolar proteinosis, pulmonary disease, chronic obstructive, pulmonary edema, pulmonary embolism, pulmonary emphysema, pulmonary fibrosis, respiratory distress syndrome, newborn-respiratory hypersensitivity, respiratory tract infections, rhinoscleroma, scimitar syndrome, severe acute respiratory syndrome, silicosis, sleep apnea, central stridor, tracheal stenosis, decreased muscle mass or bone mass due to asthma, wasting in chronic obstructive pulmonary disease (COPD), Wegener's granulomatosis, or whooping cough.

[0284] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a nervous system disease in a subject. In one embodiment, the use comprises a composition comprising a compound and an anti-cancer agent, an immunomodulating agent, an agent treating the central nervous system, an anti-infective agent, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, nervous system diseases comprise autonomic nervous system diseases, central nervous system diseases, cranial nerve diseases, demyelinating diseases, nervous system malformations, neurologic manifestations, or neuromuscular diseases.

[0285] In some embodiments, central nervous system diseases comprise injuries or damage to the central nervous system (CNS). In some embodiments, injuries or damage to the CNS may be associated with muscle wasting disorders. Injuries or damage to the CNS can be, for example, caused by diseases, trauma or chemicals. Examples are central nerve injury or damage, peripheral nerve injury or damage and spinal cord injury or damage.

[0286] Studies involving patients with spinal cord injuries (SCI) have shown that central neurotransmitters may be altered after SCI causing hypothalamus-pituitary-adrenal axis dysfunction, whose disruption led to a significant decrease in testosterone and other hormone levels. SCI or other acute illness or trauma characteristically includes heightened catabolism in conjunction with the lowered anabolic activity resulting in a condition that is prone to loss of lean body tissue, which is often accompanied by disturbed nutrient utilization. The effects of the loss of lean body mass include the development of wounds and impaired healing mechanisms, further compounding the problem. Because of poor nutrition and protein catabolism combined with immobilization, patients with spinal cord injury are at high risk for bed sores.

[0287] In one embodiment, a wide variety of injuries of the CNS may be treated by the present invention. CNS injury may refer, in one embodiment, to a breakdown of the membrane of a nerve cell, or, in another embodiment, to the inability of the nerve to produce and propagate nerve impulses, or in another embodiment, to the death of the cell. An injury includes damage that directly or indirectly affects the normal functioning of the CNS. The injury may be a structural, physical, or mechanical impairment and may be caused by physical impact, as in the case of a crushing, compression, or stretching of nerve fibers. Alternatively, the cell membrane may be destroyed by or degraded by an illness, a chemical imbalance, or a physiological malfunction such as anoxia (e.g., stroke), aneurysm, or reperfusion. A CNS injury includes, for example and without limitation, damage to retinal ganglion cells, a traumatic brain injury, a stroke-related injury, a cerebral aneurysm-related injury, a spinal cord injury, including monoplegia, diplegia, paraplegia, hemiplegia and quadriplegia, a neuroproliferative disorder, or neuropathic pain syndrome.

[0288] With injury to the spinal cord of a mammal, connections between nerves in the spinal cord are broken. Such injuries block the flow of nerve impulses for the nerve tracts affected by the injury, with a resulting impairment to both sensory and motor function. Injuries to the spinal cord may arise from compression or other contusion of the spinal cord, or a crushing or severing of the spinal cord. A severing of the spinal cord, also referred to herein as a "transection," may be a complete severing or, may be an incomplete severing of the spinal cord.

[0289] Treating a subject suffering from a CNS injury or, in other embodiments, spinal cord injury, may be accompanied by treatment of the subject with electrical stimulation of the injured site and the administration of a purine nucleoside, or analog thereof, for example as described in United States Patent Application Publication Number 20040214790A1.

[0290] In some embodiments, demyelinating diseases comprise adrenoleukodystrophy, alexander disease, canavan disease, demyelinating disease, diffuse cerebral sclerosis of schilder, leukodystrophy-globoid cell, leukodystrophy-metachromatic, multiple sclerosis, or neuromyelitis optica.

[0291] Treating a subject with a nervous system disease may encompass treating any secondary conditions in the subject, which arise due to the subject having a nervous system disease, some of which are described herein.

[0292] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with an ophthalmic disease in a subject. In one embodiment, the use comprises a composition comprising a compound and an anti-cancer agent, an immunomodulating agent, an agent treating the cardiovascular system, an anti-infective agent, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments ophthalmic disease comprise acute zonal occult outer retinopathy, Adie syndrome, albinism, ocular-amaurosis, fugax, amblyopia, aniridia, anisocoria, anophthalmos, aphakia, astigmatism, blepharitis, blepharoptosis, blepharospasm, blindness, cataract, chalazion, chorioretinitis, choroideremia, coloboma, color vision defects, conjunctivitis, corneal diseases, corneal dystrophies, corneal edema, corneal ulcer, diabetic retinopathy, diplopia, distichiasis, dry eye syndromes, Duane retraction syndrome, ectropion, entropion, esotropia, exfoliation syndrome, exotropia, eye hemorrhage, eye neoplasms, eyelid diseases, floaters, general fibrosis syndrome, glaucoma, gyrate atrophy, hemianopsia, Hermanski-Pudlak syndrome, hordeolum, Horner syndrome, hyperopia, hyphema, iritis, Kearns-Sayer syndrome, keratitis, keratoconus, lacrimal apparatus diseases, lacrimal duct obstruction, lens diseases, macular degeneration, microphthalmos, myopia, nystagmus, pathologic, ocular motility disorders, oculomotor nerve diseases, ophthalmoplegia, optic atrophies, optic nerve diseases, optic neuritis, optic neuropathy, orbital cellulitis, papilledema, peter's anomaly, presbyopia, pterygium, pupil disorders, refractive errors, retinal detachment, retinal diseases, retinal vein occlusion, retinitis pigmentosa, retinopathy of prematurity, retinoschisis, scleritis, scotoma, strabismus, Thygeson's superficial punctate keratitis, trachoma, uveitis, white dot syndrome, vision disorders, or vitreous disorders

[0293] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a urologic and/or male genital disease in a subject. In one embodiment, the use comprises a composition comprising a compound and an anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the gastrointestinal system, an anti-infective agent, an agent treating the kidney, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, an urologic and/or male genital diseases comprise anti-glomerular basement membrane disease, balanitis, bladder exstrophy, bladder neoplasms, cryptorchidism, cystitis, interstitial, diabetes insipidus, nephrogenic, epididymitis, fournier gangrene, glomerulonephritis, Goodpasture syndrome, hematospermia, hematuria, hemolytic-uremic syndrome, hydronephrosis, hypospadias, impotence, infertility, kidney calculi, kidney failure, acute, kidney failure, chronic, kidney tubular necrosis, acute, medullary sponge kidney, multicystic dysplastic kidney, nephritis, hereditary, nephrosis, nephrotic syndrome, nocturia, oliguria, penile diseases, penile induration, penile neoplasms, phimosis, priapism, prostatic diseases, benign prostate hyperplasia, prostatic neoplasms, proteinuria, pyelonephritis, Reiter disease, renal artery obstruction, spermatic cord torsion, testicular diseases, urethral stricture, urethritis, urinary retention, urinary tract infections, urination disorders, urologic and male genital diseases, urologic diseases, varicocele, vesico, or urethral reflux.

[0294] In one embodiment, the compound as described herein is useful in wound healing as an adjunct to physical

therapy/rehabilitation, or as an anabolic agent. In another embodiment, the compound as described herein is useful in promoting healing of anterior cruciate ligament (ACL) or medial cruciate ligament (MCL) injuries, or accelerating recovery after ACL or MCL surgery. In another embodiment, the compound as described herein is useful in enhancing athletic performance. In another embodiment, the compound as described herein is useful in treating burns. In another embodiment, the compound as described herein is useful in stimulating cartilage regrowth. In another embodiment, the compound as described herein is useful in preventing, treating, or reversing of catabolism associated with prolonged critical illness, pulmonary dysfunction, ventilator dependency, aging, AIDS, trauma, surgery, congestive heart failure, cardiac myopathy, burns, cancer, COPD. In another embodiment, the compound as described herein is useful in preventing or reversing protein catabolism due to trauma. In another embodiment, the compound as described herein is useful as a) adjunct to cauterization therapy (laser or radio) as is used in surgery to promote wound healing, b) adjunct to cryotherapy to promote wound healing, c) adjunct to chemotherapy to prevent side effects such as alopecia, hypogonadism, muscle wasting, osteopenia, osteoporosis, sarcopenia, increased LDL, triglyceride (TG) or total cholesterol, decreased HDL. In another embodiment, the compound as described herein is useful in chronic catabolic state (coma, wasting conditions, starvation, eating disorders); concomitant bone fracture and muscle damage; critical illness in which muscle or bone wasting are apparent; and/or connective tissue diseases and disorders.

[0295] In some embodiments, burns are associated with reduced testosterone levels, and hypogonadism is associated with delayed wound healing. In one embodiment, the compositions of this invention provide for treating a subject suffering from a wound or a burn.

[0296] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with an endocrine disorder in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound and anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating a dermatological disorder, an agent treating the central nervous system, an anti-infective agent, an agent treating the liver, an agent treating the kidney, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, endocrine disorders comprise acromegaly, Addison disease, adrenal gland diseases, adrenal hyperplasia, congenital, androgen-insensitivity syndrome, congenital hypothyroidism, Cushing syndrome, diabetes insipidus, diabetes mellitus, diabetes mellitus-type 1, diabetes mellitus-type 2, diabetic, ketoacidosis, empty Sella syndrome, endocrine gland neoplasms, endocrine system diseases, gigantism, gonadal disorders, graves disease, hermaphroditism, hyperaldosteronism, hyperglycemic hyperosmolar nonketotic coma, hyperpituitarism, hyperprolactinemia, hyperthyroidism, hypogonadism, hypopituitarism, hypothyroidism, Kallmann syndrome, Nelson syndrome, parathyroid diseases, pituitary diseases, polyendocrinopathies, autoimmune, puberty, delayed, puberty, precocious, renal osteodystrophy, thyroid diseases, thyroid hormone resistance syndrome, thyroid neoplasms, thyroid nodule, thyroiditis, thyroiditis, autoimmune, thyroiditis, subacute, or Wolfram syndrome.

[0297] In one embodiment, "Hypogonadism" is a condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development.

[0298] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with urogenital disease and/or fertility in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and anti-cancer agent, an immunomodulating agent, an anti-infective agent, an agent treating the kidney, gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, urogenital diseases and/or fertility diseases comprise abortion, spontaneous-adhesions-pelvic, candidiasis, vulvovaginal, depression-postpartum, diabetes, gestational, dyspareunia, dystocia, eclampsia, endometriosis, fetal death, fetal growth retardation, fetal membranes, premature rupture, genital diseases, female, genital neoplasms, female, hydatidiform mole, hyperemesis gravidarum, infertility, ovarian cysts, ovarian torsion, pelvic inflammatory disease, placenta diseases, placental insufficiency, polycystic ovary syndrome, polyhydramnios, postpartum hemorrhage, pregnancy complications, pregnancy, ectopic, pruritus vulvae, puerperal disorders, puerperal infection, salpingitis, trophoblastic neoplasms, uterine cervix incompetence, uterine inversion, uterine prolapse, vaginal diseases, vulvar diseases, vulvar lichen sclerosis.

[0299] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a congenital, hereditary, or neonatal disease in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating a dermatological disorder, an agent treating the central nervous system, an anti-infective agent, an agent treating the liver, an agent treating the kidney, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, congenital, hereditary, and neonatal diseases comprise Aicardi syndrome, amniotic band syndrome, anencephaly, An-

gelman syndrome, ataxia telangiectasia, Bannayan-Zonana syndrome, Barth syndrome, basal cell nevus syndrome, Beckwith-Wiedemann syndrome, bloom syndrome, branchio-oto-renal syndrome, cat eye syndrome, cerebral gigantism-charge syndrome, chromosome 16 abnormalities, chromosome 18 abnormalities, chromosome 20 abnormalities, chromosome 22 abnormalities, Costello syndrome, cri-du-chat syndrome, Currarino syndrome, cystic fibrosis, de-Lange syndrome, distal trisomy 10q, down syndrome, ectodermal dysplasia, fetal alcohol syndrome, fetal diseases, fetofetal transfusion, fragile x syndrome, Freeman-Sheldon syndrome, gastroschisis, genetic diseases, inborn, hernia, umbilical, holoprosencephaly, incontinentia pigmenti, Ivemark syndrome, Jacobsen syndrome, jaundice, Klinefelter syndrome, Larsen syndrome, Laurence-moon syndrome, lissencephaly, microcephaly, monosomy 9p, nail-patella syndrome, neurofibromatosis, neuronal ceroid-lipofuscinosis, Noonan syndrome, ochoa syndrome (urofacial syndrome, hydronephrosis with peculiar facial expression), oculocerebrorenal syndrome, Pallister-Killian syndrome, Prader-Willi syndrome, proteus syndrome, prune belly syndrome, Rett syndrome, Robinow syndrome, Rubinstein-Taybi syndrome, schizencephaly, situs inversus, Smith-Lemli-Opitz syndrome, Smith-Magenis syndrome, Sturge-Weber syndrome, syphilis, congenital, trichothiodystrophy, triple-x females, trisomy 13 (Patau syndrome), trisomy 9, turner syndrome, twins, conjoined, Usher syndrome, Waardenburg's syndrome, Werner syndrome, or Wolf-Hirschhorn syndrome.

[0300] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a metabolic disease in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and antidiabetic agent, an agent treating the gastrointestinal system, an agent treating a dermatological disorder, an agent treating the central nervous system, an anti-infective agent, an agent treating the liver, an agent treating the kidney, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, metabolic diseases comprise acid-base imbalance, acidosis, alkalosis, alkaptonuria, alpha-mannosidosis, amino acid metabolism inborn errors, amyloidosis, iron-deficiency anemia, ascorbic acid deficiency, avitaminosis, beriberi, biotinidase deficiency, carbohydrate-deficient glycoprotein syndrome, carnitine disorders, cystinosis, cystinuria, dehydration, fabry disease, fatty acid oxidation disorders, fucosidosis, galactosemias, Gaucher disease, Gilbert disease, glucosephosphate dehydrogenase deficiency, glutaric acidemia, glycogen storage disease, Hartnup disease, hemochromatosis, hemosiderosis, hepatolenticular degeneration, histidinemia, homocystinuria, hyperbilirubinemia, hypercalcemia, hyperinsulinism, hyperkalemia, hyperlipidemia, hyperoxaluria, hypervitaminosis A, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatasia, insulin resistance, iodine deficiency, iron overload, jaundice, chronic idiopathic, leigh disease, lesch-nyhan syndrome, leucine metabolism disorders, lysosomal storage diseases, magnesium deficiency, maple syrup urine disease, Melas syndrome, Menkes kinky hair syndrome, metabolic diseases, metabolic syndrome x, metabolism, inborn errors, mitochondrial diseases, mucopolidoses, mucopolysaccharidoses, Niemann-Pick diseases, obesity, ornithine carbamoyltransferase deficiency disease, osteomalacia, pellagra, peroxisomal disorders, phenylketonurias, porphyria, erythropoietic, porphyrias, progeria, pseudo-gaucher disease, refsum disease, Reye syndrome, rickets, Sandhoff disease, starvation, tangier disease, Tay-Sachs disease, tetrahydrobiopterin deficiency, trimethylaminuria, tyrosinemias, urea cycle disorders, water-electrolyte imbalance, Wernicke encephalopathy, vitamin A deficiency, vitamin B12 deficiency, vitamin B deficiency, Wolman disease, or Zellweger syndrome.

[0301] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a liver disease in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and anti-cancer agent, an immunomodulating agent, an agent treating the gastrointestinal system, an anti-infective agent, an agent treating the liver, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, liver diseases comprise liver cancer, primary biliary cirrhosis, autoimmune hepatitis, chronic liver disease, cirrhosis of the liver, hepatitis, viral hepatitis (hepatitis a, hepatitis b, chronic hepatitis b, hepatitis c, chronic hepatitis c, hepatitis d, hepatitis e, hepatitis x), liver failure, jaundice, neonatal jaundice, hepatoma, liver cancer, liver abscess, alcoholic liver disease, hemochromatosis, Wilson's disease, portal hypertension, primary sclerosing cholangitis, sarcoidosis, tapeworms, alveolar hydatid disease, fascioliasis, schistosomiasis, gaucher disease, Zellweger syndrome, alcoholism, food poisoning, pneumococcal pneumonia' or vibrio vulnificus.

[0302] In some embodiments, the present invention provides a compound or composition for treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a kidney disease in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the gastrointestinal system, an anti-infective agent, an agent treating the kidney, an agent treating a metabolic disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, kidney diseases comprise acromegaly, acute renal failure (ARF) amyloidosis, autosomal dominant polycystic kidney disease, kidney stones, kidney cysts, autosomal recessive polycystic kidney disease, chronic renal failure (CRF), chronic renal disease, coffin-Lowry syndrome, cor pulmonale, cryoglobulinemia, diabetic nephropathy, dyslipidemia, Gaucher

disease, glomerulonephritis, goodpasture syndrome, hemolytic uremic syndrome, hepatitis, kidney cancer, kidney stones, leukemia, lipoproteinemia, lupus, multiple myeloma, nephritis, polyartekidney cysts, post streptococcal glomerulonephritis, glomerulonephritis, kidney pain, preeclampsia, renal tuberculosis, pyelonephritis, renal tubular acidosis kidney disease, streptococcal toxic shock syndrome, thromboembolism, toxoplasmosis, urinary tract infections, vesicoureteral reflux, or williams syndrome.

[0303] In one embodiment, the kidney disease or disorder is acute, or in another embodiment, chronic. In one embodiment, clinical indications of a kidney disease or disorder, wherein the methods of treatment may be useful include urinary casts, measured GFR, or other markers of renal function.

[0304] In one embodiment, the compound or composition of this invention are useful in subjects predisposed to kidney diseases or disorders. In one embodiment, the phrase "predisposed to a kidney disease or disorder" with respect to a subject is synonymous with the phrase "subject at risk", and includes a subject at risk of acute or chronic renal failure, or at risk of the need for renal replacement therapy, if the subject is reasonably expected to suffer a progressive loss of renal function associated with progressive loss of functioning nephron units. Whether a particular subject is at risk is a determination which may routinely be made by one of ordinary skill in the relevant medical or veterinary art.

[0305] In one embodiment, subjects with kidney disease, in particular male subjects with end-stage renal disease (ESRD) suffer from hypogonadism, with some having concomitant moderate to severe protein-energy malnutrition (PEM), which leads to higher required doses of erythropoietin (EPO), lower quality of life (QOL) scores, and higher mortality. Many have other symptoms associated with hypogonadism, including fatigue, lack of appetite, muscle weakness, etc. In some embodiments, the treatments of this invention are useful in treating symptoms associated with hypogonadism, brought about in the subject by androgen deficiency in a female (ADIF); androgen deficiency in aging male (ADAM) to include fatigue, depression, decreased libido, erectile dysfunction, decreased cognition, decreased mood; androgen insufficiency (male or female), androgen deficiency (male or female).

[0306] In one embodiment, diabetic nephropathy is a complication of diabetes that evolves early, typically before clinical diagnosis of diabetes is made. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day or $20 \mu\text{g}/\text{min}$) of albumin in the urine (microalbuminuria), followed by albuminuria (>300 mg/24 h or $200 \mu\text{g}/\text{min}$) that develops over a period of 10-15 years. In patients with type 1 diabetes, diabetic hypertension typically becomes manifest early on, by the time that patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate (GFR) falls over a course of times, which may be several years, resulting in End Stage Renal Disease (ESRD) in diabetic individuals.

[0307] Hypertension is another comorbid factor for renal disease. In some embodiments, treatment of renal disease according to the present invention may comprise concomitant treatment with a compound of this invention and an agent which treats hypertension.

[0308] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a wasting disease in a subject. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating the central nervous system, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, vitamins, or a combination thereof. In some embodiments, wasting diseases comprise muscle injury, bed rest, immobility, nerve injury, neuropathy, diabetic neuropathy, alcoholic neuropathy, subacute combined degeneration of the spinal cord, diabetes, rheumatoid arthritis, motor neurone diseases, Duchenne muscular dystrophy, carpal tunnel syndrome, chronic infection, tuberculosis, Addison's disease, adult sma, limb muscle atrophy, alcoholic neuropathy, anorexia, anorexia nervosa, anorexia associated with cachexia, anorexia associated with aging, back tumour, dermatomyositis, hip cancer, inclusion body myositis, incontinentia pigmenti, intercostal neuralgia, juvenile rheumatoid arthritis, Legg-Calve-Perthes disease, muscle atrophy, multifocal motor neuropathy, nephrotic syndrome, osteogenesis imperfecta, post-polio syndrome, rib tumor, spinal muscular atrophy, reflex sympathetic dystrophy syndrome, or Tay-Sachs.

[0309] A wasting condition or disorder is defined herein as a condition or disorder that is characterized, at least in part, by an abnormal, progressive loss of body, organ or tissue mass. A wasting condition can occur as a result of a pathology such as, for example, cancer, or it can be due to a physiologic or metabolic state, such as disuse deconditioning that can occur, for example, due to prolonged bed rest or when a limb is immobilized, such as in a cast, or with the occurrence of multiple wounds, including, for example, amputation, as occurs in diabetics, and other conditions, as will be appreciated by one skilled in the art. A wasting condition can also be age associated. The loss of body mass that occurs during a wasting condition can be characterized by a loss of total body weight, or a loss of organ weight such as a loss of bone or muscle mass due to a decrease in tissue protein.

[0310] In one embodiment, the terms "muscle wasting" or "muscular wasting", refer to the progressive loss of muscle mass and/or to the progressive weakening and degeneration of muscles, including the skeletal or voluntary muscles which control movement, cardiac muscles which control the heart, and smooth muscles. In one embodiment, the muscle

wasting condition or disorder is a chronic muscle wasting condition or disorder. "Chronic muscle wasting" is defined herein as the chronic (i.e. persisting over a long period of time) progressive loss of muscle mass and/or to the chronic progressive weakening and degeneration of muscle.

5 [0311] The loss of muscle mass that occurs during muscle wasting can be characterized by a muscle protein breakdown or degradation, by muscle protein catabolism. Protein catabolism occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Protein catabolism or depletion, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting. The term "catabolism" has its commonly known meaning in the art, specifically an energy burning form of metabolism.

10 [0312] Muscle wasting can occur as a result of pathology, disease, condition or disorders, including disorders for treatment via this invention, such as, for example, end stage renal failure.

[0313] In some embodiments, the present invention provides a compound or composition for use in the prevention of statin induced rhabdomyolysis, organ failure or insufficiency. In some embodiments, the present invention provides a compound or composition for use in the prevention of statin induced kidney or liver failure or insufficiency. In one embodiment, the use of the present invention comprises administering to a subject a composition comprising a compound of this invention and a statin.

15 [0314] In one embodiment, the wasting disease is cachexia or involuntary weight loss in a subject. In another embodiment, the present invention provides a compound or composition for use in treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a kidney disease. In one embodiment, the present invention provides a compound or composition for use in treating, preventing, inhibiting, reducing or suppressing protein catabolism in a subject suffering from a kidney disease or disorder.

20 [0315] Cachexia is weakness and a loss of weight caused by a disease or as a side effect of illness. Long term hospitalization due to illness or injury, or disuse deconditioning that occurs, for example, when a limb is immobilized, can also lead to muscle wasting. Studies have shown that in patients suffering injuries, chronic illnesses, burns, trauma or cancer, who are hospitalized for long periods of time, there is a long-lasting unilateral muscle wasting, with a consequent decrease in body mass. Nervous system injury, for example, spinal cord injury, as described further herein, may be a contributory factor, as well.

25 [0316] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a wasting diseases or disorders in a subject. In another embodiment, the wasting diseases and disorders include *inter-alia* : a) acquired immunodeficiency syndrome (AIDS) wasting; b) wasting associated with bed rest; c) bulimia, and/or wasting associated with bulimia; c) cachexia; d) cancer cachexia; e) HIV wasting; f) reduce cachexia and protein loss due to prolonged critical illness, pulmonary dysfunction, ventilator dependency, aging, AIDS, trauma, surgery, congestive heart failure, cardiac myopathy, burns, cancer, chronic obstructive pulmonary disease (COPD), eating disorders such bulimia, anorexia nervosa, loss of appetite, starvation, and/or depression.

30 [0317] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a hypogonadal state in a subject. In one embodiment, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a pharmacotherapy induced hypogonadal state in a subject. In some embodiments, hypogonadism is caused by treatments which alter the secretion of hormones from the sex glands in both women and men. In some embodiments, hypogonadism may be "primary" or "central". In primary hypogonadism, the ovaries or testes themselves do not function properly. In some embodiments, hypogonadism may be induced by surgery, radiation, genetic and developmental disorders, liver and kidney disease, infection, or certain autoimmune disorders. In some embodiments, menopause is a form of hypogonadism. Menopause may cause, in some embodiments, amenorrhea, hot flashes, vaginal dryness, or irritability due to woman's estrogen levels fall. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and an anti-cancer agent, an immunomodulating agent, an anti-diabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating the central nervous system, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, an agent treating a dermatological disorder, an anti-infective agent, an agent treating the liver, an agent treating the kidney, vitamins, or a combination thereof.

35 [0318] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with osteopenic state in a subject. In one embodiment, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a pharmacotherapy induced osteopenic state in a subject. In some embodiments, osteopenia is a mild thinning of the bone mass. In some embodiments, osteopenia is a precursor to osteoporosis. In some embodiments osteopenia is defined as a bone density between one standard deviation (SD) and 2.5 SD below the bone density of a normal young

adult. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and an anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating the central nervous system, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, an agent treating a dermatological disorder, an anti-infective agent, an agent treating the liver, an agent treating the kidney, vitamins, or a combination thereof.

[0319] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a sarcopenic state in a subject. In one embodiment, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a pharmacotherapy induced sarcopenic state in a subject. In some embodiments, sarcopenia is a significant loss of muscle mass. In one embodiment, sarcopenia definition is having a lean body mass less than two standard deviation below the mean for normal young adults. In some embodiments, sarcopenia is caused by genetic factors, altered circulation, decrease in the capillary:muscle fiber ratio, altered motor neurons, denervation, deterioration of motor end plates, selective reinnervation of Type I fibers, inflammatory responses causing muscle damage, reduced exercise, malnutrition, low dietary protein intake, vitamin D deficiency, age-related decline in vitamin D, oxidative stress, muscle mitochondrial mutations, changes in specific types of muscle fibers, decline in muscle protein, disabling disease, strokes, Alzheimer's disease, Parkinson's disease, osteoporosis, atherosclerosis, diabetes mellitus, hyperinsulinemia, renal failure, or hypogonadism. In one embodiment, the use comprises administering to a subject a composition comprising a SARM compound and an anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating the central nervous system, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, an agent treating a dermatological disorder, an anti-infective agent, an agent treating the liver, an agent treating the kidney, vitamins, or a combination thereof.

[0320] In some embodiments, the present invention provides a compound or composition for use in treating, reducing the incidence, delaying the onset or progression, or reducing and/or abrogating the symptoms associated with a combination of diseases and/or disorders in a subject as described hereinabove. In one embodiment, the use comprises administering to a subject a composition comprising a compound of this invention and an anti-cancer agent, an immunomodulating agent, an antidiabetic agent, an agent treating the cardiovascular system, an agent treating the gastrointestinal system, an agent treating the central nervous system, an agent treating a metabolic disease, an agent treating a wasting disease, a gene therapy agent, an agent treating the endocrine system, an agent treating a dermatological disorder, an anti-infective agent, an agent treating the liver, an agent treating the kidney, vitamins, or a combination thereof.

[0321] It is to be understood that any use of this invention, as herein described, encompasses the administration of a compound as herein described, or a composition comprising the same, to the subject, in order to treat the indicated disease, disorder or condition. The treatments as herein described each and/or all may further comprise administration of an additional therapeutic agent as herein described, and as will be appreciated by one skilled in the art.

[0322] Also disclosed is a method for enhanced production such as milk, sperm, or egg. In some embodiments, the present invention provides a method for enhanced production of lean meats or eggs. In some embodiments, the present invention provides a method for increased productivity of feeds or stud livestock, for example, increased sperm count, improved morphology of sperm, etc. In some embodiments, the present invention provides a method for expanding the productive life of farm animals, for example, egg-laying hens, milk-producing cows, etc, and/or enhanced herd health, for example, improved immune clearance, stronger animals.

[0323] In another embodiment, this invention provides a compound or composition for use in treating a hormone dependent disease, disorder or condition, the treatment comprising administering to the subject a compound as herein described, and optionally chemotherapeutics agents and therapies (methotrexate, cyclophosphamide, ifosfamide, adriamycin, doxorubicin, glucocorticoids, cyclosporine, L-thyroxine, SERMs, AI, fulvestrant, GnRH agents, ADT, discontinuation of hormone replacement therapy, cranial irradiation, peripheral irradiation, etc.; prolactinemia-inducing pharmacotherapeutics (serotonergic antidepressants acting through 5HT2 receptors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, antihypertensives such as methyl dopa, reserpine, clonidine, and verapamil; antidopaminergic anti-emetics such as metoclopramide, H2 receptor antagonists such as cimetidine and ranitidine, estrogens, amphetamines, AR partial antagonists (ketoconazole, spironolactone, eplerenone)

[0324] In another embodiment, the compounds of this invention and compositions as described herein are useful in promoting or speeding recovery following a surgical procedure.

[0325] In one embodiment, the present invention provides a compound as described herein for use in reducing a fat mass in a subject.

[0326] In another embodiment, this invention provides a compound as described herein or a composition comprising the same for use in treating abdominal fat accumulation; treating obese sarcopenia; improving body composition; lowering body fat content; lowering fat mass; improving blood lipid profile, increasing muscle mass/strength/function; increasing

bone mass/BMD/strength/function; lowering body fat; or treating congenital hyperinsulinemia, cushing's disease (hyper-cortisolemia), obesity or diabetes associated with a metabolic syndrome in a subject.

[0327] In another embodiment, the subject has a hormonal imbalance, disorder, or disease. In another embodiment the subject has menopause.

[0328] In one embodiment, the present invention provides a compound as described herein for use in increasing a lean mass in a subject.

[0329] In one embodiment the subject has a hormonal imbalance, disorder, or disease. In another embodiment the subject has menopause.

[0330] Example 5 demonstrates that a compound of formula S-(I) is anabolic yet minimally androgenic, thus such compounds may be useful in treating patient groups in which androgens were contraindicated in the past. Compound of formula S-(I) was shown to stimulate muscle growth, whether in the presence or absence of testosterone while exerting anti-proliferative effects on the prostate, thus, in one embodiment, this invention provides for restoring lost muscle mass in patients with sarcopenia or cachexia.

[0331] In one embodiment, the compounds as herein described alter the levels of leptin in a subject. In another embodiment, the compounds as herein described decrease the levels of leptin. In another embodiment, the compounds as herein described increase the levels of leptin in a subject. Leptin is known to have an effect on appetite on weight loss in obese mice, and thus has been implicated in obesity.

[0332] The compounds as herein described, in one embodiment, affect circulating, or in another embodiment, tissue levels of leptin. In one embodiment, the term 'level/s of leptin' refers to the serum level of leptin. As contemplated herein, the compounds of the present invention have an effect on leptin *in-vitro* and *in-vivo*. Leptin levels can be measured by methods known to one skilled in the art, for example by commercially available ELISA kits. In addition, leptin levels may be determined in *in-vitro* assays, or in *in-vivo* assays, by any method known to a person skilled in the art.

[0333] Since leptin is implicated in controlling appetite, weight loss, food intake, and energy expenditure, modulating and/or controlling the levels of leptin is a useful therapeutic approach in treating preventing, inhibiting or reducing the incidence of obesity in subjects suffering from obesity. Modulating the level of leptin can result in a loss of appetite, a reduction of food intake, and an increase in energy expenditure in the subject, and thus may contribute to the control and treatment of obesity.

[0334] The term "obesity" is defined, in one embodiment, as an increase in body weight beyond the limitation of skeletal and physical requirement, as the result of excessive accumulation of fat in the body.

[0335] The term "obesity-associated metabolic disorder" refers, in one embodiment, to a disorder which results from, is a consequence of, is exacerbated by or is secondary to obesity. Non-limiting examples of such a disorder are osteoarthritis, type II diabetes mellitus, increased blood pressure, stroke, and heart disease.

[0336] Cholesterol, triacylglycerol and other lipids are transported in body fluids by lipoproteins which may be classified according to their density, for example, the very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).

[0337] It has been shown that high levels of LDL-cholesterol in the blood correlate with atherosclerosis which is a progressive disease characterized in part by sedimentation of lipids in inner walls of arteries, particularly of coronary arteries. It has also been shown that a high blood level of LDL- cholesterol correlates with coronary heart disease. Also, a negative correlation exists between blood levels of HDL cholesterol and coronary heart disease.

[0338] The level of total cholesterol in blood, which is the sum of HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol and chylomicron-cholesterol, is not necessarily predictive of the risk of coronary heart disease and atherosclerosis.

[0339] The correlation between atherosclerosis and LDL cholesterol levels, however, is much higher than a similar correlation between atherosclerosis and total serum cholesterol levels.

[0340] Disclosed herein is the use of the compounds as herein described for improving the lipid profile and/or reducing the circulating lipid levels in a subject. In some embodiments, the subject suffers from one or more conditions selected from the group consisting of: atherosclerosis and its associated diseases, premature aging, Alzheimer's disease, stroke, toxic hepatitis, viral hepatitis, peripheral vascular insufficiency, renal disease, and hyperglycemia, and the invention provides for the administration of a compound or composition comprising the same, as herein described, which in some embodiments positively affects a lipid profile in the subject, which is one means by which the invention is useful in treating the indicated diseases, disorders and conditions.

[0341] Disclosed herein is a compound for use in the treatment of atherosclerosis and its associated diseases, such as for example, cardiovascular disorders, cerebrovascular disorders, peripheral vascular disorders, intestinal vascular disorders, or combinations thereof.

[0342] In one embodiment cardiovascular disorders comprise of hypertension (HTN), coronary artery disease (CAD) or myocardial perfusion. In another embodiment this invention provides a SARM compound as herein described for use in promoting aortic smooth muscle cell proliferation. In another embodiment this invention provides the compound as herein described for use in treating arteriosclerosis. In another embodiment this invention provides the compound as herein described for use in lowering blood pressure. In another embodiment this invention provides use of the compounds

as herein described for treating cardiac diseases and disorders comprising cardiomyopathy, cardiac dysfunctions such as myocardial infarction, cardiac hypertrophy and cognitive heart failure. In another embodiment this invention provides use of the compounds as herein described for cardioprotection comprising cardioprotection in insulin resistance; treating diabetes type I and II, metabolic syndrome, syndrome X and/or high blood pressure.

5 **[0343]** Disclosed herein is a compound of formula S-(I) or composition comprising the same for use in treating, preventing, reducing the risk of mortality from cardiovascular and/or cerebrovascular disease in a subject.

[0344] In one embodiment, compounds of formulae S-(I) reduce LDL and total cholesterol levels.

10 **[0345]** In another embodiment, compounds of formulae S-(I) are co-administered with HDL-elevating agents. In another embodiment, HDL-elevating agents include niacin. In another embodiment the HDL-elevating agents include fibrates including gemfibrozil (Lopid®), thiourea based gemfibrozil analogues, and fenofibrate (TriCor). In another embodiment, HDL-elevating agents include statins. In another embodiment, HDL-elevating agents include 1-hydroxyalkyl-3-phenylthiourea, and analogs thereof.

15 **[0346]** Disclosed herein is a compound of formula S-(I) or composition comprising the same for use in reducing circulating lipid levels in a subject. In one embodiment, the subject suffers from atherosclerosis and its associated diseases, premature aging, Alzheimer's disease, stroke, toxic hepatitis, viral hepatitis, peripheral vascular insufficiency, renal disease, hyperglycemia, or any combination thereof.

20 **[0347]** Disclosed herein is a compound of formula S-(I) or composition comprising the same for use in treating atherosclerosis and its associated diseases, such as, for example, cardiovascular disorders, cerebrovascular disorders, peripheral vascular disorders, or intestinal vascular disorders in a subject. The treatment may further comprise co-administration, subsequent or prior administration with an agent or agents, which are known to be useful in treating cardiovascular disorders, cerebrovascular disorders, peripheral vascular disorders, or intestinal vascular disorders.

[0348] The term "diabetes", in one embodiment, refers to a relative or absolute lack of insulin leading to uncontrolled carbohydrate metabolism. Most patients can be clinically classified as having either insulin-dependent diabetes mellitus (IDDM or type-I diabetes) or non-insulin-dependent diabetes mellitus (NIDDM or type-II diabetes).

25 **[0349]** The term "increased blood pressure" or "hypertension" refers, in other embodiments, to a repeatedly high blood pressure above 140 over 90 mmHg. Chronically-elevated blood pressure can cause blood vessel changes in the back of the eye, thickening of the heart muscle, kidney failure, and brain damage.

30 **[0350]** The term "stroke" refers, in other embodiments, to damage to nerve cells in the brain due to insufficient blood supply often caused by a bursting blood vessel or a blood clot. The term "heart disease", in other embodiments, refers to a malfunction in the heart normal function and activity, including heart failure.

[0351] In addition, androgens have recently been shown to be involved in commitment of mesenchymal pluripotent cells into myogenic lineage and to block differentiation into adipogenic lineage (Singh et al., Endocrinology, 2003, Jul 24). Accordingly, the compounds can be useful in methods of blocking adipogenesis, and/or altering stem cell differentiation, as described herein.

35 **[0352]** In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in promoting, increasing or facilitating weight loss in a subject.

[0353] In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in decreasing, suppressing, inhibiting or reducing appetite of a subject.

40 **[0354]** In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in altering the body composition of a subject. In one embodiment, altering the body composition comprises altering the lean body mass, the fat free body mass of the subject, or a combination thereof.

[0355] In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in altering lean body mass or fat free body mass of a subject.

45 **[0356]** In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in converting fat to lean muscle in a subject.

[0357] In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in treating an obesity-associated metabolic disorder in a subject.

[0358] In another embodiment, this invention relates to a compound of formula S-(I) or composition comprising the same for use in preventing, suppressing, inhibiting or reducing an obesity-associated metabolic disorder in a subject.

50 **[0359]** In one embodiment, the obesity-associated metabolic disorder is hypertension. In another embodiment, the disorder is osteoarthritis. In another embodiment, the disorder is type II diabetes mellitus. In another embodiment, the disorder is increased blood pressure. In another embodiment, the disorder is stroke. In another embodiment, the disorder is heart disease.

55 **[0360]** Also disclosed is a compound of formula S-(I) or composition comprising the same for use in decreasing, suppressing, inhibiting or reducing adipogenesis in a subject.

[0361] It is disclosed that the compounds as herein described are useful in a) treating, preventing, suppressing, inhibiting, or reducing obesity; b) promoting, increasing or facilitating weight loss; c) decreasing, suppressing, inhibiting or reducing appetite; d) altering the body composition; e) altering lean body mass or fat free body mass; f) converting

fat to lean muscle; g) treating, preventing, suppressing, inhibiting, or reducing an obesity-associated metabolic disorder, for example hypertension, osteoarthritis, diabetes mellitus, maturity onset diabetes of the young (MODY), increased blood pressure, stroke, or heart disease; h) decreasing, suppressing, inhibiting or reducing adipogenesis; i) altering stem cell differentiation; and/or j) altering the level of leptin.

5 **[0362]** In one embodiment, the compounds as herein described find utility in treating or halting the progression of, or treating symptoms of diabetes. In another embodiment, the compounds as herein described are useful in treating co-morbidities related to diabetes. These conditions include: hypertension (HTN), cerebrovascular disease, atherosclerotic coronary artery disease, macular degeneration, diabetic retinopathy (eye disease) and blindness, cataracts--systemic inflammation (characterized by elevation of inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein), birth defects, pregnancy related diabetes, pre-eclampsia and hypertension in pregnancy, kidney disease (renal insufficiency, renal failure etc.), nerve disease (diabetic neuropathy), superficial and systemic fungal infections, congestive heart failure, gout/hyperuricemia, obesity, hypertriglyceridemia, hypercholesterolemia, fatty liver disease (non-alcoholic steatohepatitis, or NASH), and diabetes-related skin diseases such as Necrobiosis Lipoidica Diabeticorum (NLD), Blisters of diabetes (Bullosis Diabeticorum), Eruptive Xanthomatosis, Digital Sclerosis, Disseminated Granuloma Annulare, and Acanthosis Nigricans.

10 **[0363]** In one embodiment this invention provides a compound of formula S-(I) or composition comprising the same for use in treating, suppressing, inhibiting or reducing the incidence of (a) diabetes type I; (b) diabetes type II; (c) glucose intolerance; (d) hyperinsulinemia; (e) insulin resistance (f) nephropathy; (g) diabetic neuropathy; (h) diabetic retinopathy (i) fatty liver conditions (j) MODY and (k) cardiovascular disease in a human subject.

20 **[0364]** In some embodiments, the compounds as herein described and/or compositions comprising the same may be used for treating diseases or conditions associated with a subject having diabetes. In one embodiment, the subject for whom treatment is sought is one with diabetic I. Type I diabetes is characterized by autoimmune destruction of pancreatic beta-cells. Markers of immune destruction of the beta-cell are present at the time of diagnosis in 90% of individuals and include antibodies to the islet cell (ICAs), to glutamic acid decarboxylase (GAD), and to insulin (IAAs). While this form of diabetes usually occurs in children and adolescents, it can occur at any age. Younger individuals typically have a rapid rate of beta-cell destruction and present with ketoacidosis, while adults often maintain sufficient insulin secretion to prevent ketoacidosis for many years. Eventually, all type I diabetic patients require insulin therapy to maintain normoglycemia.

25 **[0365]** In one embodiment, this invention provides a compound or composition for use in treating diabetes type II. Type II diabetes is characterized by insulin resistance and at some stage in pathogenesis of the disease, a relative deficiency of insulin secretion. In absolute terms, the plasma insulin concentration (both fasting and meal-stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis. With time, however, there is progressive beta cell failure and absolute insulin deficiency ensues. Most individuals with type II diabetes exhibit intra abdominal (visceral) obesity, fatty liver, which is closely related to the presence of insulin resistance. The patient's liver becomes insulin resistant and glycogen breakdown is uncontrolled and the result is increased and unphysiological glucose delivery to the bloodstream. The liver generated cholesterol and VLDL particles is also uncontrolled. In addition, hypertension, dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipemia), and elevated PAI-1 levels often are present in these individuals. This clustering of abnormalities is referred to as the "insulin resistance syndrome", or the "metabolic syndrome" or obesity related disorders. Because of these abnormalities, patients with type II diabetes are at increased risk of developing macrovascular complications such as myocardial infarction and stroke.

30 **[0366]** In one embodiment, this invention provides a compound or composition for use in treating diabetic nephropathy. Diabetic nephropathy is a complication of diabetes that evolves early, typically before clinical diagnosis of diabetes is made. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day or 20 μ g/min) of albumin in the urine (microalbuminuria), followed by albuminuria (>300 mg/24 h or 200 μ g/min) that develops over a period of 10-15 years. In patients with type 1 diabetes, diabetic hypertension typically becomes manifest early on, by the time that patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate (GFR) falls over a course of times, which may be several years, resulting in end stage renal disease (ESRD) in diabetic individuals.

35 **[0367]** In one embodiment, this invention provides a compound or composition for use in treating diabetic neuropathy. Diabetic neuropathy is a family of nerve disorders caused by diabetes. Diabetic neuropathies cause numbness and sometimes pain and weakness in the hands, arms, feet, and legs. Neurologic problems in diabetes may occur in every organ system, including the digestive tract, heart, and genitalia. Diabetic neuropathies are classified as peripheral, autonomic, proximal, and focal. Peripheral neuropathy causes pain or loss of feeling in the toes, feet, legs, hands, and arms. Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration and can also affect the nerves that serve the heart and control blood pressure. Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs. Focal neuropathy results in the sudden weakness of one nerve, or a group of nerves, causing muscle weakness or pain. Any nerve in the body may be affected.

[0368] In one embodiment, this invention provides a compound or composition for use in treating diabetic retinopathy. The effect of diabetes on the eye is called diabetic retinopathy. Patients with diabetes are more likely to develop eye problems such as cataracts and glaucoma. The affect of diabetic retinopathy on vision varies widely, depending on the stage of the disease. Some common symptoms of diabetic retinopathy are blurred vision (this is often linked to blood sugar levels), floaters and flashes and sudden loss of vision.

[0369] In one embodiment, the subject for whom treatment is sought via the the invention is one with glucose intolerance. Glucose intolerance is a pre-diabetic state in which the blood glucose is higher than normal but not high enough to warrant the diagnosis of diabetes.

[0370] In one embodiment, the subject for whom treatment is sought is one with hyperinsulinemia. Hyperinsulinemia is a sign of an underlying problem that is causing the pancreas to secrete excessive amounts of insulin. The most common cause of hyperinsulinemia is insulin resistance, a condition in which your body is resistant to the effects of insulin and the pancreas tries to compensate by making more insulin. hyperinsulinemia is associated with type II diabetes

[0371] In one embodiment, the subject for whom treatment is sought is one with insulin resistance. Insulin resistance is a condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to the metabolic syndrome and type II diabetes.

[0372] Diabetes and the liver obesity is typically associated with elevated levels of free fatty acid (FFAs) that promote lipid accumulation and insulin resistance in target tissues, i.e. reduced action of insulin primarily in skeletal muscle and liver. A prominent role of insulin is to reduce glucose output from the liver. FFAs stimulate hepatic gluconeogenesis which per se does not lead to increased hepatic glucose output as long as it is paralleled by a decrease in hepatic glycogenolysis, a compensatory process referred to as "hepatic autoregulation". FFAs stimulate insulin secretion and insulin blocks glycogenolysis in part by inhibiting secretion of glucagon, an inducer of glycogenolysis. However, long-term elevated levels of FFAs leads to hepatic insulin resistance and thus breakdown of hepatic autoregulation, resulting in increased hepatic glucose production and development of type II diabetes. Fatty liver and hepatic insulin resistance is a major driving force behind hyperglycemia and type II diabetes.

[0373] In one embodiment, this invention provides a compound or composition that inhibit (improve) the fatty liver, resulting in that the insulin resistance in the liver is inhibited (improved) and thereby solving the basic problem in type II diabetes.

[0374] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating suppressing, inhibiting or reducing the incidence of diabetes is a human subject, comprising the step of administering to said subject a compound of formula I or a pharmaceutically acceptable salt thereof.

[0375] In another embodiment, the diabetes is a Type I diabetes. In another embodiment, the diabetes is a type II diabetes.

[0376] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating a human subject having glucose intolerance.

[0377] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating hyperinsulinemia in a human subject.

[0378] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating insulin resistance in a human subject.

[0379] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating diabetic nephropathy in a human subject.

[0380] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating diabetic neuropathy in a human subject.

[0381] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating diabetic retinopathy in a human subject.

[0382] In one embodiment, this invention provides a compound of formula S-(I) or composition comprising the same for use in treating fatty liver conditions in a human subject.

[0383] In one embodiment this invention provides a compound of formula S-(I) or composition comprising the same for use in a) treating, preventing, suppressing or inhibiting atherosclerosis b) treating, preventing, suppressing or inhibiting liver damage due to fat deposits comprising the step of administering to the subject a compound as described herein, or a composition comprising the same, in an amount effective to treat, prevent or inhibit atherosclerosis and liver damage due to fat deposit.

[0384] In one embodiment atherosclerosis refers to a slow, complex disease that may begin with damage to the innermost layer of the artery. In another embodiment the causes of damage to the arterial wall may include a) elevated levels of cholesterol and in the blood; b) high blood pressure; c) tobacco smoke d) diabetes. In another embodiment, the condition is treatable in a smoker, despite the fact that tobacco smoke may greatly worsen atherosclerosis and speed

its growth in the coronary arteries, the aorta and arteries in the legs. Similarly, in another embodiment, this invention may be useful in treating subjects with a family history of premature cardiovascular disease who have an increased risk of atherosclerosis.

5 **[0385]** In one embodiment, liver damage due to fat deposits refer to the build-up of fat in the liver cells forming a fatty liver which may be associated with or may lead to inflammation of the liver. This can cause scarring and hardening of the liver. When scarring becomes extensive, it is called cirrhosis.

[0386] In another embodiment the fat accumulates in the liver as obesity. In another embodiment fatty liver is also associated with diabetes mellitus, high blood triglycerides, and the heavy use of alcohol. In another embodiment fatty liver may occur with certain illnesses such as tuberculosis and malnutrition, intestinal bypass surgery for obesity, excess
10 vitamin A in the body, or the use of certain drugs such as valproic acid (trade names: Depakene/Depakote) and corticosteroids (cortisone, prednisone). Sometimes fatty liver occurs as a complication of pregnancy.

[0387] In one embodiment, subjects with kidney disease, in particular male subjects with end-stage renal disease (ESRD) suffer from hypogonadism, with some having concomitant moderate to severe protein-energy malnutrition (PEM), which leads to higher required doses of EPO, lower QOL scores, and higher mortality. Many have other symptoms
15 associated with hypogonadism, including fatigue, lack of appetite, muscle weakness, etc. In some embodiments, the treatments of this invention are useful in treating symptoms associated with hypogonadism, brought about in the subject by the kidney disease or disorder.

[0388] In one embodiment, diabetic nephropathy is a complication of diabetes that evolves early, typically before clinical diagnosis of diabetes is made. The earliest clinical evidence of nephropathy is the appearance of low but abnormal
20 levels (>30 mg/day or 20 μ g/min) of albumin in the urine (microalbuminuria), followed by albuminuria (>300 mg/24 h or 200 μ g/min) that develops over a period of 10-15 years. In patients with type 1 diabetes, diabetic hypertension typically becomes manifest early on, by the time that patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate (GFR) falls over a course of times, which may be several years, resulting in End Stage Renal Disease (ESRD) in diabetic individuals.

25 **[0389]** Hypertension is another comorbid factor for renal disease. In some embodiments, treatment of renal disease according to the present invention may comprise concomitant treatment with a compound of this invention and an agent which treats hypertension.

[0390] Androgen-dependent conditions which may be treated with the compounds and/or compositions as herein described include those conditions which are associated with aging. In one embodiment, the compound as described
30 herein is useful in a) Age-related functional decline (ARFD); b) reversal or prevention of ARFD; c) reversal or prevention of ARFD in elderly d) reversal or prevention of ARFD-induced sarcopenia or osteopenia; e) andropause, andropausal vasomotor symptoms, f) andropausal gynecomastia, muscle strength/function; g) bone strength/function; h) anger; i) asthenia; j) chronic fatigue syndrome; k) cognitive impairment; and/or 1) improving cognitive function.

[0391] In one embodiment, the compound as described herein is useful in treating inflammation and related disorders
35 such as a) prevention, treatment, or reversal of arthritis; b) prevention, treatment, or reversal of an arthritic condition such as Behcet's disease (autoimmune vasculitis), bursitis, calcium pyrophosphate dihydrate crystal (CPPD), deposition disease (or pseudogout), carpal tunnel syndrome, connective tissue disorders, Crohn's diseases, Ehlers-Danlos syndrome (EDS), fibromyalgia, gout, infectious arthritis, inflammatory bowel disease (IBD), juvenile arthritis, systemic lupus erythematosus (SLE), Lyme's disease, Marfan syndrome, myositis, osteoarthritis, polyarteritis nodosa, polymyalgia rheumatica, psoriasis, psoriatic arthritis, Raynaud's phenomenon, reflex sympathetic dystrophy syndrome, Reiter's syndrome,
40 rheumatoid arthritis, scleroderma, Sjögrens' syndrome, tendonitis or ulcerative colitis; c) preventing, treatment, or reversing an autoimmune disease.

[0392] In one embodiment, the compound as described herein is useful in prevention of iatrogenic effects comprising acute fatigue syndrome (post-surgical) or androgen-deprivation therapy (ADT) induced side effects such as reduced
45 muscle mass, reduced muscle strength, frailty, hypogonadism, osteoporosis, osteopenia, decreased BMD and/or decreased bone mass.

[0393] In one embodiment, the compounds and/or compositions and/or uses thereof are for the treatment of human subjects, wherein, in one embodiment, the subject is male, or in another embodiment, the subject is female.

[0394] In one embodiment, the use of the present invention comprises administering a compound of this invention as
50 the sole active ingredient. However, also encompassed within the scope of the present invention are treatments for diabetes and related disorders, hormone therapy, dry eye, obesity, treating prostate cancer, delaying the progression of prostate cancer, and for preventing and/or treating the recurrence of prostate cancer, male contraception; treatment of osteoporosis, treatment of conditions associated with ADIF and for treatment and/or prevention of chronic muscular wasting which comprise administering the compounds in combination with one or more therapeutic agents. These agents
55 include LHRH analogs, reversible antiandrogens, antiestrogens, anticancer drugs, 5-alpha reductase inhibitors, aromatase inhibitors, progestins, agents acting through other nuclear hormone receptors, selective estrogen receptor modulators (SERM), progesterone, estrogen, PDE5 inhibitors, apomorphine, bisphosphonate, and one or more additional SARMs.

[0395] Thus, in one embodiment, the use of the present invention comprises administering the compound of this invention in combination with diabetes drug such as troglitazone, rosiglitazone, and pioglitazone. In another embodiment, the use of the present invention comprises administering the compound in combination with an LHRH analog. In another embodiment, the use of the present invention comprises administering the compound, in combination with a reversible antiandrogen. In another embodiment, the use of the present invention comprises administering the compound, in combination with an antiestrogen. In another embodiment, the use of the present invention comprises administering the compound, in combination with an anticancer drug. In another embodiment, the use of the present invention comprises administering the compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the use of the present invention comprises administering the compound, in combination with an aromatase inhibitor. In another embodiment, the use of the present invention comprises administering the compound, in combination with a progestin. In another embodiment, the use of the present invention comprises administering the compound, in combination with an agent acting through other nuclear hormone receptors. In another embodiment, the use of the present invention comprises administering the compound, in combination with a selective estrogen receptor modulator (SERM). In another embodiment, the use of the present invention comprises administering the compound, in combination with a progesterone. In another embodiment, the use of the present invention comprises administering the compound, in combination with an estrogen. In another embodiment, the use of the present invention comprises administering the compound, in combination with a PDE5 inhibitor. In another embodiment, the use of the present invention comprises administering the compound, in combination with apomorphine. In another embodiment, the use of the present invention comprises administering the compound, in combination with a bisphosphonate. In another embodiment, the use of the present invention comprises administering the compound, in combination with one or more additional SARMs. In some embodiments, the use of the present invention comprises combined preparations comprising the compound and an agent as described hereinabove. In some embodiments, the combined preparations can be varied, e.g., in order to cope with the needs of a patient subpopulation to be treated or the needs of the single patient which different needs can be due to the particular disease, severity of the disease, age, sex, or body weight as can be readily determined by a person skilled in the art. In some embodiments, the use of the present invention comprises personalized medicine methods which treat the needs of a single patient. In one embodiment, different needs can be due to the particular disease, severity of the disease, the overall medical state of a patient, or the age of the patient. In some embodiments, personalized medicine is the application of genomic data to better target the delivery of medical interventions. Methods of personalized medicine, in some embodiments, serve as a tool in the discovery and clinical testing of new products of the present invention. In one embodiment, personalized medicine involves the application of clinically useful diagnostic tools that may help determine a patient's predisposition to a particular disease or condition. In some embodiments, personalized medicine is a comprehensive approach utilizing molecular analysis of both patients and healthy individuals to guide decisions throughout all stages of the discovery and development of pharmaceuticals and diagnostics; and applying this knowledge in clinical practice for a more efficient delivery of accurate and quality healthcare through improved prevention, diagnosis, treatment, and monitoring methods.

[0396] The compounds of this invention, characterized by the structure of the formula S-(I) exhibited partial progesterone receptor (PR) agonist activity. In some embodiments, the compound or composition of this invention is provided for treatment of a disease or condition, which may be alleviated or improved by the administration of a PR agonist, by administration of a compound represented by the structure S-(I). In one embodiment the compound of formula S-(I) may be administered in an amount effective for the following applications: regulating menses; treating or preventing a benign progestin-dependent condition, such as endometriosis, leiomyoma, ovarian cysts, premenstrual syndrome, anemia, dysmenorrhea, or pelvic inflammatory disease; or treating a progestin-responsive tumor, such as a breast carcinoma, an ovarian carcinoma, a prostate carcinoma, an endometrial carcinoma, a cervical carcinoma, a leiomyosarcoma, or a meningioma.

[0397] In some embodiments, the compound or composition of this invention is provided for the treatment or amelioration of a progestin-dependent disease or condition. In some embodiments, the term "progestin-dependent disease" or "progestin-dependent condition" refers to an affliction, disorder, or physiological state that depends upon progestin activity for its existence or that is exacerbated by progestin activity.

[0398] In some embodiments, the compound or composition of this invention is provided for the treatment or amelioration of a progestin-responsive tumor. In some embodiments, the term "progestin-responsive tumor" refers to a tumor that contains progesterone receptors and whose growth and/or metastatic potential is stimulated by the binding of progestin to progesterone receptors within the tumor.

[0399] In some embodiments, the compound of formula S-(I) may be effective to regulate fertility during the female reproductive cycle of an animal or human, or in some embodiments, to control irregularities in the human menstrual cycle or to synchronize or repress the fertile periods of commercial animals (e.g., fish, cows, sheep, pigs, goats, or chickens), laboratory animals (e.g., apes, chimpanzees, rats, mice, or guinea pigs), or domestic animals (dogs, cats, ferrets, birds, rabbits, or horses). In some embodiments, the compound of formula S-(I) may be effective to lessen menstrual flow, thereby being useful in the treatment or prevention of anemia and dysmenorrhea. In some embodiments,

the compound of formula S-(I) may be effective for the prevention or treatment of premenstrual syndrome, endometriosis, leiomyoma (uterine fibroids), and/or ovarian cysts. In addition, in a subject that has or has previously had pelvic inflammatory disease, in which scarring of the fallopian tubes may have occurred, the compound of formula S-(I) may be used to lessen the chance that a tubal pregnancy may occur.

[0400] In some embodiments, the compound of formula S-(I) may be effective to prevent pregnancy. Such administration, in some embodiments, may be prior to ovulation or prior to coitus, or after ovulation or after coitus. In some embodiments, such administration inhibits implantation of an embryo in the subject or in some embodiments, inhibits ovulation in the subject.

[0401] In some embodiments, the compound of formula S-(I) may be administered in an amount effective to induce cervical ripening in a female. The cervical ripening may be preparatory to labor and delivery of offspring, or preparatory to dilatation and curettage. In another embodiment, such administration is carried out in order to induce expulsion of an embryo or fetus from the subject.

[0402] In some embodiments, for applications directed to its PR agonist activity, the compound of formula S-(I) may be administered alone, or as part of a pharmaceutical composition and the compound and/or composition comprising the same may be understood to comprise any embodiment as herein described. The skilled artisan will readily appreciate routes of administration most suitable for treating the conditions related thereto, and as such represent embodiments herein. Similarly, dosaging, timing of administration, and other aspects of treatment with reference to treating progesterin-dependent diseases or conditions may comprise any embodiment of treatment as described herein, including what is encompassed by the term "treatment" as herein described.

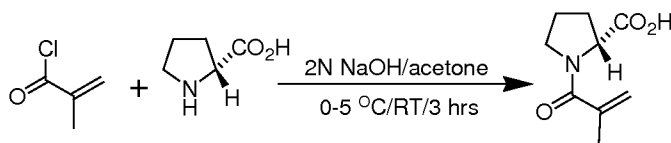
[0403] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXAMPLES

EXAMPLE 1

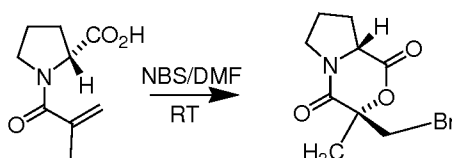
Synthesis of (S) Enantiomer of Compound of Formula (I) (Figures 1A-1L)

[0404]



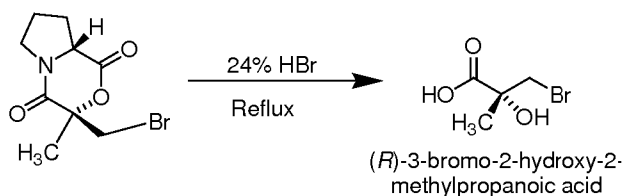
[0405] (2R)-1-Methacryloylpyrrolidin-2-carboxylic Acid. *D*-Proline, 14.93 g, 0.13 mol) was dissolved in 71 mL of 2 N NaOH and cooled in an ice bath; the resulting alkaline solution was diluted with acetone (71 mL). An acetone solution (71 mL) of methacryloyl chloride (13.56 g, 0.13 mol) and 2N NaOH solution (71 mL) were simultaneously added over 40 min to the aqueous solution of *D*-proline in an ice bath. The pH of the mixture was kept at 10-11°C during the addition of the methacryloyl chloride. After stirring (3 h, room temperature), the mixture was evaporated *in vacuo* at a temperature at 35-45 °C to remove acetone. The resulting solution was washed with ethyl ether and was acidified to pH 2 with concentrated HCl. The acidic mixture was saturated with NaCl and was extracted with EtOAc (100 mL x 3). The combined extracts were dried over Na₂SO₄, filtered through Celite®, and evaporated *in vacuo* to give the crude product as a colorless oil. Recrystallization of the oil from ethyl ether and hexanes afforded 16.2 (68%) of the desired compound as colorless crystals: mp 102-103 °C (lit. [214] mp 102.5-103.5 °C); the NMR spectrum of this compound demonstrated the existence of two rotamers of the title compound. ¹H NMR (300 MHz, DMSO-d₆) δ 5.28 (s) and 5.15 (s) for the first rotamer, 5.15 (s) and 5.03 (s) for the second rotamer (totally 2H for both rotamers, vinyl CH₂), 4.48-4.44 for the first rotamer, 4.24-4.20 (m) for the second rotamer (totally 1H for both rotamers, CH at the chiral center), 3.57-3.38 (m, 2H, CH₂), 2.27-2.12 (1H, CH), 1.97-1.72 (m, 6H, CH₂, CH, Me); ¹³C NMR (75 MHz, DMSO-d₆) δ for major rotamer 173.3, 169.1, 140.9, 116.4, 58.3, 48.7, 28.9, 24.7, 19.5; for minor rotamer 174.0, 170.0, 141.6, 115.2, 60.3, 45.9, 31.0, 22.3, 19.7; IR (KBr) 3437 (OH), 1737 (C=O), 1647 (CO, COOH), 1584, 1508, 1459, 1369, 1348, 1178 cm⁻¹; [α]_D²⁶ +80.8° (c = 1, MeOH); Anal. Calcd. for C₉H₁₃NO₃: C 59.00, H 7.15, N 7.65. Found: C 59.13, H 7.19, N 7.61.

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[0406] (3R,8aR)-3-Bromomethyl-3-methyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazine-1,4-dione. A solution of NBS (23.5 g, 0.132 mol) in 100 mL of DMF was added dropwise to a stirred solution of the (methyl-acryloyl)-pyrrolidine (16.1 g, 88 mmol) in 70 mL of DMF under argon at room temperature, and the resulting mixture was stirred 3 days. The solvent was removed *in vacuo*, and a yellow solid was precipitated. The solid was suspended in water, stirred overnight at room temperature, filtered, and dried to give 18.6 g (81%) (smaller weight when dried ~ 34%) of the title compound as a yellow solid: mp 152-154 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 4.69 (dd, *J* = 9.6 Hz, *J* = 6.7 Hz, 1H, CH at the chiral center), 4.02 (d, *J* = 11.4 Hz, 1H, CHH_a), 3.86 (d, *J* = 11.4 Hz, 1H, CHH_b), 3.53-3.24 (m, 4H, CH₂), 2.30-2.20 (m, 1H, CH), 2.04-1.72 (m, 3H, CH₂ and CH), 1.56 (s, 2H, Me); ¹³C NMR (75 MHz, DMSO-d₆) δ 167.3, 163.1, 83.9, 57.2, 45.4, 37.8, 29.0, 22.9, 21.6; IR (KBr) 3474, 1745 (C=O), 1687 (C=O), 1448, 1377, 1360, 1308, 1227, 1159, 1062 cm⁻¹; [α]_D²⁶ +124.5 ° (c = 1.3, chloroform); Anal. Calcd. for C₉H₁₂BrNO₃: C 41.24, H 4.61, N 5.34. Found: C 41.46, H 4.64, N 5.32.

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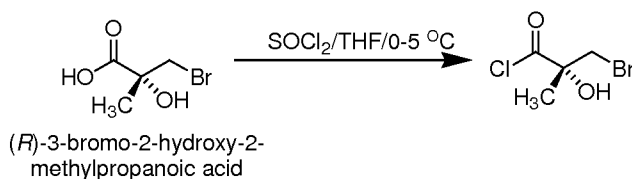


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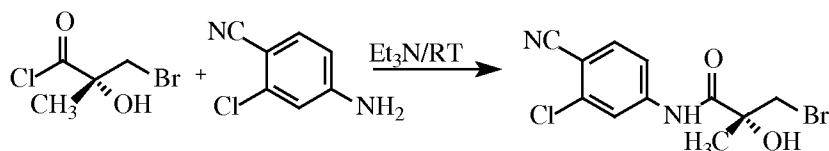
[0407] (2R)-3-Bromo-2-hydroxy-2-methylpropanoic Acid. A mixture of bromolactone (18.5 g, 71 mmol) in 300 mL of 24% HBr was heated at reflux for 1 h. The resulting solution was diluted with brine (200 mL), and was extracted with ethyl acetate (100 mL x 4). The combined extracts were washed with saturated NaHCO₃ (100 mL x 4). The aqueous solution was acidified with concentrated HCl to pH = 1, which, in turn, was extracted with ethyl acetate (100 mL x 4). The combined organic solution was dried over Na₂SO₄, filtered through Celite®, and evaporated *in vacuo* to dryness. Recrystallization from toluene afforded 10.2 g (86%) of the desired compound as colorless crystals: mp 107-109 °C (lit. [214] mp 109-113 °C for the *S*-isomer); ¹H NMR (300 MHz, DMSO-d₆) δ 3.63 (d, *J* = 10.1 Hz, 1H, CHH_a), 3.52 (d, *J* = 10.1 Hz, 1H, CHH_b), 1.35 (s, 3H, Me); IR (KBr) 3434 (OH), 3300-2500 (COOH), 1730 (C=O), 1449, 1421, 1380, 1292, 1193, 1085 cm⁻¹; [α]_D²⁶ +10.5° (c = 2.6, MeOH); Anal. Calcd. for C₄H₇BrO₃: C 26.25, H 3.86. Found: C 26.28, H 3.75.

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**R-18**

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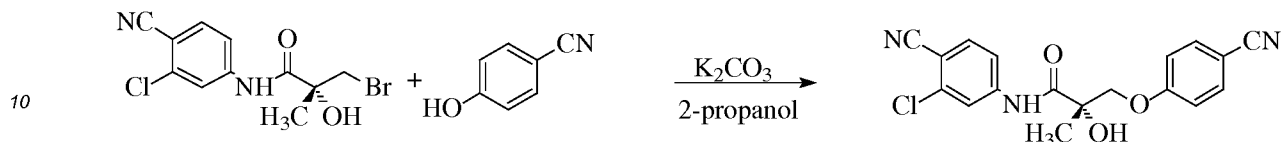
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[0408] Synthesis of (2R)-3-bromo-N-(3-chloro-4-cyanophenyl)-2-hydroxy-2-methylpropanamide. Thionyl chloride (7.8 g, 65.5 mmol) was added dropwise to a cooled solution (less than 4 °C) of (R)-3-bromo-2-hydroxy-2-methylpropanoic acid (9.0 g, 49.2 mol) in 50 mL of THF under an argon atmosphere. The resulting mixture was stirred for 3 h under the same condition. To this was added Et₃N (6.6 g, 65.5 mol) and stirred for 20 min under the same condition. After 20 min, 4-amino-2-chlorobenzonitrile (5.0 g, 32.8 mmol) and 100 mL of THF were added and then the mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure to give a solid which was treated with 100 mL of H₂O, extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with

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saturated NaHCO₃ solution (2 × 100 mL) and brine (300 mL), successively. The organic layer was dried over MgSO₄ and concentrated under reduced pressure to give a solid which was purified from column chromatography using EtOAc/hexane (50:50) to give 7.7 g (49.4%) of target compound as a brown solid.

[0409] ¹H NMR (CDCl₃/TMS) δ 1.7 (s, 3H, CH₃), 3.0 (s, 1H, OH), 3.7 (d, 1H, CH), 4.0 (d, 1H, CH), 7.5 (d, 1H, ArH), 7.7 (d, 1H, ArH), 8.0 (s, 1H, ArH), 8.8 (s, 1H, NH). MS:342.1 (M+23). Mp 129°C.



[0410] **Synthesis of (S)-N-(3-chloro-4-cyanophenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide.** A mixture of bromoamide (2.0 g, 6.3 mmol), anhydrous K₂CO₃ (2.6 g, 18.9 mmol) in 50 mL of acetone was heated to reflux for 2 h and then concentrated under reduced pressure to give a solid. The resulting solid was treated with 4-cyanophenol (1.1 g, 9.5 mmol) and anhydrous K₂CO₃ (1.7 g, 12.6 mmol) in 50 mL of 2-propanol to reflux for 3 h and then concentrated under reduced pressure to give a solid. The residue was treated with 100 mL of H₂O and then extracted with EtOAc (2 X 100 mL). The combined EtOAc extracts were washed with 10% NaOH (4 X 100 mL) and brine, successively. The organic layer was dried over MgSO₄ and then concentrated under reduced pressure to give an oil which was purified by column chromatography using EtOAc/hexane (50:50) to give a solid. The solid was recrystallized from CH₂Cl₂/hexane to give 1.4 g (61.6 %) of (S)-N-(3-chloro-4-cyanophenyl)-3-(4-cyanophenoxy)-2-hydroxy-2-methylpropanamide as a colorless solid.

[0411] ¹H NMR (CDCl₃/TMS) δ 1.61 (s, 3H, CH₃), 3.25 (s, 1H, OH), 4.06 (d, J = 9.15 Hz, 1H, CH), 4.50 (d, J = 9.15 Hz, 1H, CH), 6.97 - 6.99 (m, 2H, ArH), 7.53-7.59 (m, 4H, ArH), 7.97 (d, J = 2.01 Hz, 1H, ArH), 8.96 (s, 1H, NH). Calculated Mass: 355.1, [M+Na]⁺ 378.0. Mp: 103-105 °C.

EXAMPLE 2

Inhibition of Cytochrome P450 Enzymes

[0412] CYP enzymes are a super-family of heme proteins located in the smooth endoplasmic reticulum of cells. These enzymes have wide substrate specificity, and are the major group of enzymes responsible for drug metabolism

[0413] CYP inhibition screening assays were performed for S-(I), S-(II) and S-(III). In order to assess whether S-(I) exhibited any inhibitory effects on CYP activity, the five major isoenzymes of the CYP family were evaluated *in vitro*. Human recombinant CYP enzymes and fluorescence-based substrates were used to determine the IC₅₀ values of S-(I) against CYP3A4, 2D6, 2C19, 2C9, and 1A2.

Materials and Methods:

Recombinant Enzyme (Fluorescent-based) Assay

[0414] CYP inhibition screening procedures were performed essentially according to the manufacturer's instructions (Gentest, BD Biosciences, Waltham, MA). Briefly, CYP enzyme inhibition was measured using human cDNA-expressed CYP3A4, 2D6, 2C19, 2C9, and 1A2 enzymes. Analogs of the model substrate coumarin were utilized for each isoenzyme. 7-Benzyloxy-trifluoromethylcoumarin (BFC) for 3A4; 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC) for 2D6; 3-cyano-7-ethoxycoumarin (CEC) for 2C19 and 1A2; and 7-methoxy-4-trifluoro-methylcoumarin (MFC) for 2C9. These substrates were utilized at a single concentration (either 50 μM or 75 μM) at or near the apparent K_m for each substrate. The positive control inhibitors used for inhibition assays are shown in Table 1.

[0415] Compound stocks (10 mM in a 4:1 ratio of acetonitrile:DMSO, or neat acetonitrile) were prepared and diluted to provide an 8-point dose response curve in duplicate (final concentration ranging from 0.15 μM to 20.0 μM). The concentration of acetonitrile was kept constant at 0.4%, and the reaction was carried out at 37°C for 30 minutes. An IC₅₀ value was calculated as the concentration where 50% inhibition of the catalytic activity of the enzyme occurs.

Table 1. Profile of Positive Control Inhibitors.

Compound	CYP Inhibition, IC ₅₀ (μM)				
	3A4	2D6	2C19	2C9	1A2
Ketoconazole	0.006				
Quinidine		0.012			
Tranlycypromine			3.4		
Sulfaphenazole				0.33	
Furafylline					2.5

Analytical Methods

[0416] Fluorescent intensity was measured using a Wallac 1420 Victor³ Multi-label Counter Model (Perkin-Elmer, Wellesley, MA), with an excitation wavelength filter of 405 nm, and an emission filter of 460 nm (535 nm for the 3A4 and 2C9 substrates). Nunc-brand optical bottom, black 96-well plates (#265301) were used in all assays, and a top read of 1.0 second per well was performed for all samples.

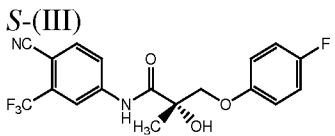
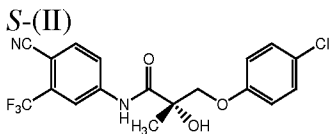
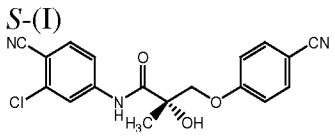
Data analysis

[0417] Duplicate averages (minus background) were determined in *Excel*, and IC₅₀ values were calculated in *GraphPad Prism*, v 4.03. For IC₅₀ determination, data was fitted using the non-linear regression equation "sigmoidal dose response, variable slope" defined as: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{-(\text{LogEC}_{50} - X) * \text{HillSlope}})$ where X is the logarithm of concentration of the indicated compound, and Y is the response.

Results:

[0418] Ketoconazole, quinidine, tranlycypromine, sulfaphenazole, and furafylline potently inhibited CYP3A4, CYP2D6, CYP2C19, CYP2C9, and CYP1A2 activity, respectively, demonstrating the utility of this *in vitro* CYP screening assay to identify compounds with the potential for significant CYP-mediated drug:drug interactions. None of the investigational substituted acylanilide compounds significantly inhibited CYP3A4, CYP2D6, or CYP1A2, indicating that drug:drug interactions via these CYP isozymes are unlikely to occur. Although all of the investigational substituted acylanilide compounds inhibited CYP2C9 activity to a modest extent, none of the compounds demonstrated potency similar to sulfaphenazole. Unexpectedly, only S-(I) failed to inhibit CYP2C19.

Table 2. CYP Inhibition Profile of Novel SARMs and Positive Controls.

Compound	CYP Inhibition, IC ₅₀ (μM)				
	3A4	2D6	2C19	2C9	1A2
S-(III) 	> 20	> 20	0.1	1.3	> 20
S-(II) 	> 20	> 20	0.1	3.8	> 20
S-(I) 	> 20	> 20	> 20	5.1	> 20
Ketoconazole	0.03				

(continued)

Compound	CYP Inhibition, IC ₅₀ (μM)				
	3A4	2D6	2C19	2C9	1A2
Quinidine		0.013			
Tranlylcypromine			11.2		
Sulfaphenazole				0.36	
Furafylline					2.02

Conclusions:

[0419] S-(II) and S-(III) demonstrated moderate inhibition of CYP2C9 and CYP2C19. Unexpectedly, S-(I) did not appreciably inhibit CYP2C19 or CYP2C9, indicating S-(I)'s unique clinical and therapeutic advantage.

EXAMPLE 3**Androgen Receptor Binding Affinity of SARMs:**Materials and Methods:

[0420] The androgen receptor (AR) binding affinity of SARMs was determined by using an *in vitro* competitive radioligand binding assay with [17α-methyl-³H]-mibolerone ([³H]MIB, PerkinElmer), a high affinity AR ligand. Recombinant androgen receptor ligand binding domain (AR LBD) was combined with [³H]MIB in buffer A (10 mM Tris, pH 7.4, 1.6 mM disodium EDTA, 0.26 M sucrose, 10 mM sodium molybdate, 1 mM PMSF) to determine the equilibrium dissociation constant (K_d) of [³H]MIB. Protein was incubated with increasing concentrations of [³H]MIB with and without a high concentration of unlabeled MIB in order to determine total and non-specific binding. Non-specific binding was then subtracted from total binding to determine specific binding and graphed using SigmaPlot® and non-linear regression for ligand binding curve with one site saturation to determine the K_d of MIB (1.84 nM). In addition, the concentration of [³H]MIB required to saturate AR LBD was determined to be 4 nM.

[0421] The S isomer of the compound of formula (I) (S-(I)) was tested in a range of concentrations from 10⁻¹¹ to 10⁻⁶ M using the conditions described above. Following incubation, plates were harvested with GF/B filters on the Unifilter-96 Harvester (PerkinElmer) and washed three times with ice-cold buffer B (60 mM Tris, pH 7.2). The filter plates were dried at RT, then 36 μl Microscint-O cocktail was added to each well and sealed with TopSeal-A. The receptor bound radioligand was then determined with the TopCount® NXT Microplate Scintillation Counter (PerkinElmer).

[0422] The specific binding of [³H]MIB at each concentration of SARM was determined by subtracting the nonspecific binding of [³H]MIB (determined by incubating with 10⁻⁶ M unlabeled MIB), and expressed as a percentage of the specific binding in the absence of each SARM. The concentration of SARM required to decrease the [³H]MIB binding by 60%, IC₆₀ value, was determined by computer-fitting the data with SigmaPlot® and non-linear regression with the standard curve four parameter logistic curve. The equilibrium binding constant (K_i) of each compound was then determined with the following equation:

$$K_i = K_d \times IC_{60} / (K_d + L)$$

where K_d is the equilibrium dissociation constant of [³H]MIB (1.84 nM), and L is the concentration of [³H]MIB (4 nM).

Results:

[0423] The binding affinity for compound of formula (I) [S-(I)] was tested in the radioligand binding assay with AR LBD as the receptor with K_i (nM) = 36.9.

EXAMPLE 4

Cross-Reactivity of S-(I) with Other Nuclear Hormone Receptors

5 **[0424]** In order to determine whether the substituted acylanilide compound of this invention affected other nuclear hormone receptor signaling, its comparative ability to stimulate (agonist) or inhibit (antagonist) ER α -, ER β -, GR-, PR-, or MR-mediated transcriptional activation, was compared to other acylanilides.

Materials and Methods:

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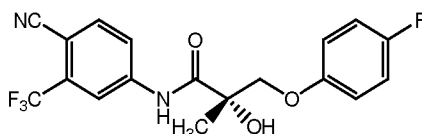
Transient Transfection

15 **[0425]** Rat GR, MR, PR, ER- α and ER- β were individually cloned into a pCR3.1 vector backbone. Sequencing was performed to verify the absence of any mutations. HEK-293 cells were plated at 90,000 cells per well of a 24 well plate in Dulbecco's Minimal Essential Media supplemented with 5% charcoal-stripped FBS. The cells were transfected using Lipofectamine (Invitrogen, Carlsbad, CA) with 0.25 μ g GRE-LUC for GR, MR and PR and ERE-LUC for ER- α and ER- β , 0.5 ng CMV-LUC (renilla luciferase) and 12.5-25 ng of the respective expression vector for each receptor. The cells were treated 24 hrs after transfection with investigational substituted acylanilide SARM compounds (S-(I), S-(II) and S-(III)) in the absence (agonist mode) and presence (antagonist mode) of known agonists (estradiol for ER; dexamethasone for GR; aldosterone for MR; progesterone for PR) as controls. Luciferase assays were performed 48 hrs after transfection. Transcriptional activation values are represented as firefly luciferase normalized to renilla luciferase.

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Results:25 Results of S-(III):**[0426]**

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35 **[0427]** The agonist effects of S-(III) on ER- β , ER- α , GR, PR and MR were tested and compared to the activities of the known ligands. As shown in Figure 2, S-(III) failed to activate ER- β or ER- α even at the highest tested concentration (1 μ M) whereas 1 nM estradiol induced ER α - and ER β -mediated transactivation by 3- and 5-fold, respectively. Figure 2 also shows the inability of S-(III) to activate PR-, GR- or MR-mediated transactivation. S-(III) at all the tested concentrations did not induce PR-, GR- or MR-mediated transactivation, whereas the known ligands (dexamethasone, progesterone and aldosterone) induced the activities of GR, PR or MR by 70- 23- and 60-fold, respectively, at a concentration of 1 nM.

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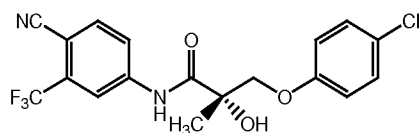
[0428] Similarly, the ability of S-(III) to inhibit the effects of a known agonist for each of the above mentioned receptors was tested.

[0429] Figure 3 summarizes the antagonist effects of S-(III) on ER- β -, ER- α -, GR-, PR- and MR-mediated transactivation. HEK-293 cells transfected with the indicated receptor and corresponding reporter construct were treated with a titration of S-(III) and then with 1 nM estradiol for ER- β and ER- α transactivation, 1 nM aldosterone for MR transactivation, 1 nM dexamethasone for GR transactivation or 1 nM progesterone for PR transactivation. Estradiol increased ER- β - and ER- α -mediated transactivation by 3- and 5-fold, respectively. Co-incubation of cells with a titration of S-(III) failed to alter the estradiol-induced ER- β or ER- α activity. Similarly, dexamethasone-induced GR-mediated transactivation and aldosterone-induced MR-mediated transactivation were not inhibited by S-(III) at any tested concentrations.

50

[0430] S-(III) significantly inhibited PR activity, however, at the highest concentrations (i.e., 1 and 10 μ M), indicating that it could function as a PR antagonist, yet RU486 (a known PR antagonist) completely inhibited PR activity at a 1 nM concentration, indicating about 10,000 fold weaker antagonistic activity for S-(III) as compared to RU486.

55 Results of S-(II):**[0431]**



5

[0432] The agonist effects of S-(II) on ER- β , ER- α , GR, PR and MR were tested and compared to the activities of the known ligands. Similar to S-(III), as shown in Figure 4, S-(II) failed to activate ER- β or ER- α even at the highest tested concentration (1 μ M) whereas 1 nM estradiol induced ER α - and ER β -mediated transactivation by 3- and 5-fold, respectively. Figure 4 also shows the inability of S-(II) to activate PR-, GR- or MR-mediated transactivation. S-(II) at all the tested concentrations did not induce PR-, GR- or MR-mediated transactivation, whereas the known ligands (dexamethasone, progesterone and aldosterone) induced the activities of GR, PR or MR by 70- 23- and 60-fold, respectively, at a concentration of 1 nM.

[0433] The ability of S-(II) to inhibit the effects of a known agonist for each of the above mentioned receptors was evaluated as well.

[0434] Figure 5 summarizes the antagonist effects of S-(II) on ER- β -, ER- α -, GR-, PR- and MR-mediated transactivation. HEK-293 cells transfected with the indicated receptor were treated with the indicated concentration of S-(II), and the known agonist for the appropriate receptor, as above. Estradiol increased ER- β - and ER- α -mediated transactivation by 3- and 5-fold, respectively. Co-incubation of cells with a titration of S-(II) failed to alter the estradiol-induced ER- β or ER- α activity. Similarly, dexamethasone-induced GR-mediated transactivation and aldosterone-induced MR-mediated transactivation were not inhibited by S-(II) at any tested concentrations. As was the case with S-(III), S-(II) failed to antagonize the ER, GR or MR, under these conditions, at the concentrations tested.

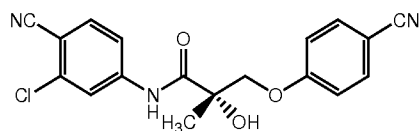
[0435] S-(II), similar to S-(III) significantly inhibited PR activity at the highest concentrations (i.e., 1 and 10 μ M) tested, however it too exhibited about 10,000 fold weaker antagonistic activity in comparison to RU486. GTX-830 [should be GTX-832?, i.e S-(II)] as compared to RU486.

25

Results of S-(I):

[0436]

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[0437] The agonist effects of S-(I) on ER- β , ER- α , GR, PR and MR were tested and compared to the activities of the known ligands, as well (Figure 6). S-(I) failed to activate ER- β or ER- α even at the highest tested concentration (1 μ M) whereas 1 nM estradiol induced ER α - and ER β -mediated transactivation by 3- and 5-fold, respectively. S-(I) failed to activate PR-, GR- or MR-mediated transactivation. S-(I) at all the tested concentrations did not induce GR- or MR-mediated transactivation, whereas the known ligands (dexamethasone, and aldosterone) induced the activities of GR or MR by 70- and 60-fold, respectively, at a concentration of 1 nM. However, S-(I) increased the transactivation of PR at 1 μ M and 10 μ M by 3 and 8 fold respectively. Progesterone activated PR by 23 fold at a 1 nM concentration, indicating that S-(I) is greater than 10,000-fold weaker than the endogenous agonist for PR.

[0438] The ability of S-(I) to inhibit the effects of a known agonist for each of the above mentioned receptors was tested as well, as in S-(II) and S-(III).

[0439] Co-incubation of HEK 293 cells with the indicated concentrations of S-(I) failed to alter the estradiol-induced ER- β or ER- α activity, dexamethasone-induced GR-mediated transactivation or aldosterone-induced MR-mediated transactivation.

[0440] Unlike S-(II) and S-(III), while S-(I) significantly partially inhibited PR activity at concentrations 0.1 μ M and 10 μ M, it completely inhibited PR-mediated transactivation at 1 μ M. In comparison to RU486, S-(I) was about 1,000 fold weaker a PR antagonist, than RU486.

[0441] S-(II) and S-(III) were found to be specific for the AR, failing to stimulate or inhibit receptor-mediated transactivation of ER α , ER β , GR, or MR. S-(II) and S-(III), and being extremely weak antagonists for PR, requiring concentrations approximately 10,000 fold higher than RU486 to inhibit PR-mediated transcriptional activation.

55

[0442] S-(I) is similarly specific for the AR and does not stimulate or inhibit receptor-mediated transactivation of ER α , ER β , GR, or MR. Unexpectedly, S-(I) exhibited partial agonist activity for PR.

EXAMPLE 5**Preclinical Anabolic and Androgenic Pharmacology of S-(I) in Intact and Castrate Male Rats.**

5 **[0443]** Anabolic and androgenic efficacy of compound of formula (I) administered by daily oral gavage were tested. The S-isomer of compound (I) [S-(I)] was synthesized and tested as described herein

Materials and Methods:

10 **[0444]** Male Sprague-Dawley rats weighing approximately 200 g were purchased from Harlan Bioproducts for Science (Indianapolis, IN). The animals were maintained on a 12-h light/dark cycle with food (7012C LM-485 Mouse/Rat Sterilizable Diet, Harlan Teklad, Madison, WI) and water available *ad libitum*. The animal protocol was reviewed and approved by the Institutional Animal Care and The anabolic and androgenic activity of compounds of formula (I) in intact animals was tested, as well as a dose response evaluation in acutely orchidectomized (ORX) animals. Regenerative effects of
15 the compound of formula (I) in chronically (9 days) ORX rats was similarly evaluated.

[0445] The test article for this study was weighed and dissolved in 10% DMSO (Fisher) diluted with PEG 300 (Acros Organics, NJ) for preparation of the appropriate dosage concentrations. The animals were housed in groups of 2 to 3 animals per cage. Animals were randomly assigned to one of seven groups consisting of 4 to 5 animals per group. Control groups (intact and ORX) were administered vehicle daily. Compound of formula (I) was administered via oral
20 gavage at doses of 0.01, 0.03, 0.1, 0.3, 0.75, and 1 mg/day to both intact and ORX groups. Where appropriate, animals were castrated on day one of the study. Treatment with compound of formula S-(I) began nine days post ORX and was administered daily via oral gavage for fourteen days.

[0446] The animals were sacrificed under anesthesia (ketamine/xylazine, 87:13 mg/kg) and body weights were recorded. In addition, ventral prostate, seminal vesicles, and levator ani muscle were removed, individually weighed,
25 normalized to body weight, and expressed as a percentage of intact control. Student's T-test was used to compare individual dose groups to the intact control group. Significance was defined *a priori* as a P-value < 0.05. Ventral prostate and seminal vesicle weights were evaluated as a measure of androgenic activity, whereas levator ani muscle weight was evaluated as a measure of anabolic activity. Blood was collected from the abdominal aorta, centrifuged, and sera were frozen at -80°C prior to determination of serum hormone levels. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations were determined.
30

Results:

35 **[0447]** A series of dose-response studies in intact and castrated rats in order to evaluate the potency and efficacy of compound of formula S-(I) in both androgenic (prostate and seminal vesicles) and anabolic (levator ani muscle) tissue was conducted. In intact animals, compound of formula (I) treatment resulted in decreases in the weight of both prostate and seminal vesicles while the levator ani muscle weight was significantly increased. Levator ani muscle weight following Compound (I) treatment were 107% ± 5%, 103% ± 7%, 97% ± 7%, 103% ± 5%, 118% ± 7%, and 118% ± 7% of intact controls following doses of 0.01, 0.03, 0.1, 0.3, 0.75, and 1 mg/day, respectively. The prostate weights were 103% ± 10%, 99% ± 10%, 58% ± 10%, 58% ± 15%, 65% ± 20%, and 77% ± 23% of intact controls following doses of 0.01,
40 0.03, 0.1, 0.3, 0.75, and 1 mg/day, respectively. These results are significant since current androgen therapies are contraindicated in some patient populations due to the proliferative androgenic effects in prostate and breast tissues. However, many patients in these populations could benefit from the anabolic actions of androgens in muscle and bone. Since compound of formula S-(I) exhibited tissue selective anabolic effects, it may be possible to treat patient groups
45 in which androgens were contraindicated in the past.

[0448] In castrated, ORX animals, prostate weights following compound S-(I) treatment were 12% ± 2%, 17% ± 6%, 31% ± 3%, 43% ± 15%, 54% ± 17%, 58% ± 10%, and 73% ± 12% of intact controls following doses of 0, 0.01, 0.03, 0.1, 0.3, 0.75, and 1 mg/day, respectively (Figure 8). Similarly, seminal vesicle weights were 10% ± 2%, 10% ± 3%, 13% ± 4%, 21% ± 6%, 43% ± 8%, 51% ± 9%, and 69% ± 14% of intact controls following doses of 0, 0.01, 0.03, 0.1,
50 0.3, 0.75, and 1 mg/day, respectively (Figure 8). Significant increases were seen in levator ani muscle weights in all dose groups, when compared to intact controls. The levator ani muscle weights were 40% ± 5%, 52% ± 8%, 67% ± 9%, 98% ± 10%, 103% ± 12%, 105% ± 12% and 110% ± 17% of intact controls corresponding to 0, 0.01, 0.03, 0.1, 0.3, 0.75, and 1.0 mg/day dose groups, respectively (Figure 8).

[0449] Testosterone propionate (TP) and S-3-(4-Acetylamino-phenoxy)-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethylphenyl) propionamide (S-4), maximally stimulated the levator ani muscle weight to 104% and 101%, respectively. These data show that compound of formula S-(I) exhibited significantly greater efficacy and potency than either TP or S-4. As a whole, these data show that compound of formula S-(I) is able to stimulate muscle growth in the presence or
55 absence of testosterone while exerting anti-proliferative effects on the prostate. These data show that the compound of

formula S-(I) restores lost muscle mass in patients with sarcopenia or cachexia. Additionally, the antiproliferative effects of the compound of formula S-(I) on the prostate may allow some patient populations, in which androgens are currently contraindicated, access to anabolic agents.

[0450] Anabolic ratios were derived comparing muscle/prostate weight in castrated rats. Values obtained were 3.02, 2.13, 2.27, 1.90, 1.83 and 1.51 following doses of 0.01, 0.03, 0.1, 0.3, 0.75 and 1 mg/day, respectively.

[0451] Animals receiving 1 mg/day of compound S-(I) exhibited a prostate weight of $77\% \pm 23\%$ and levator ani muscle weight of $118\% \pm 7\%$ of intact control values, respectively. Compound of formula S-(I) maintained prostate weight following orchidectomy at $73 \pm 12\%$ of intact controls and levator ani muscle weight at $110 \pm 17\%$ of intact controls. A derived dose of 0.1 mg/day of Compound S-(I) would restore levator ani muscle weight to 100%, while such dose would only restore $43 \pm 15\%$ prostate weight.

EXAMPLE 6

Metabolic Stability of Compound S-I:

[0452] Metabolic stability assays were performed in order to assess the *in vitro* half-life of the compound of formula S-(I) when incubated with human liver microsomes. Intrinsic clearance values were extrapolated. Permeability of the compound across human, intestinal epithelial monolayers (Caco-2 cells) was assessed as a measure of intestinal permeability as well as an indicator of efflux potential. Caco-2 cells are often used as an early screening surrogate for oral bioavailability. Microsomal half-life can be converted to *in vitro* clearance values as a means to predict hepatic intrinsic clearance. Intrinsic clearance is defined as the functional ability of the liver to metabolize a drug or other compound.

Materials and Methods:

Metabolic Stability Measured in Human Liver Microsomes:

[0453] Compounds of formula S-(I) in this study were incubated at a final concentration of 0.6 μ M. Microsome reactions were performed under either Phase I or "Phase I and II" conditions, where indicated. Compound stocks (10 mM ACN) were initially diluted to a concentration of 60 μ M (in 60% ACN/H₂O) resulting in a "working stock" solution of 100X. Human liver microsomes were utilized at a final concentration of 0.6 mg/ml. Duplicate wells were used for each time point (0, 6, 10, 30, and 60 minutes). Reactions were carried out at 37°C in a shaking water bath, and the final concentration of solvent was kept constant at 0.6%. The final volume for each reaction was 600 μ l, comprised of 368 μ l of 100 mM KPO₄ buffer, (pH 7.4); 12.6 μ l of HLM (from a 20 mg/ml stock); 6 μ l of 100X "working stock" drug compound, and 126 μ l of NRS "master mix" solution. At each time point, 100 μ l of reaction was removed and added to a sample well containing 100 μ l of ice-cold, 100% ACN (plus internal standards), to stop the reaction. The NRS "master mix" is a solution of glucose 6-phosphate dehydrogenase, NADP⁺, MgCl₂, and glucose 6-phosphate, prepared per manufacturer's instructions (BD Biosciences, Waltham, MA). Each 6.0 ml stock of NRS "master mix" solution contains 3.8 ml H₂O, 1.0 ml solution "A" (Cat. #461220), and 0.2 ml solution "B" (Cat. #461200). Human liver microsomes (lot #0610279, Xenotech Corp.) represented a pool of 60 donors.

[0454] Samples were centrifuged at 3,000 rpm for 10 minutes at 4°C to remove debris and precipitated protein. Approximately 160 μ l of supernatant was subsequently transferred to a new sample block for analysis. The concentration of parent drug remaining in each well (expressed as percent remaining versus Time '0', at the beginning of the reaction) was measured by LC/MS, as detailed below. The intrinsic clearance rates (CL_{int}) were calculated from 0 - 60 minutes based on first order decay kinetics as a function of microsomal protein concentration.

Permeability across Human, Intestinal Epithelial Monolayers:

[0455] Permeability was measured in the Apical (pH 6.6) to Basolateral (pH 7.4) and Basolateral (pH 7.4) to Apical (pH 6.6) directions across polarized, Caco-2 epithelial monolayers. Compound stocks (10 mM acetonitrile) were tested in the study at a final concentration of 10 μ M. The concentration of drug in the receiver well was measured by LC/MS/MS using a standard curve. The apparent permeability (P_{app}) for each compound was calculated, and values (A-B) were classified as: Poor (P_{app} < 1), Low (P_{app} 1-2), Medium (P_{app} 2-10) or High (P_{app} >10).

$$P_{app} (x 10^{-6} \text{ cm/sec}) = \text{Amount transported} / (\text{Area} * \text{Initial concentration} * \text{Time})$$

$$Papp \text{ (cm/s)} = [V / (A * C_i)] * (C_f / T)$$

V = volume of the receptor chamber (ml, or cm³)

A = area of the membrane insert (cm²)

C_i = initial concentration of drug (μM)

C_f = final concentration of drug (μM)

T = assay time (seconds)

10 Analytical Methods:

[0456] All samples were analyzed on the MDS/Sciex API4000 Q Trap system with electrospray ionization (ESI) in the positive or negative SIM mode, depending on the compounds. The mobile phases were isocratic at 30% A (0.1 % formic acid in water) and 70% B (0.1 % formic acid in acetonitrile) with a flow rate of 0.4 mL/min. A Phenomenex Luna Phenyl-Hexyl column (60 x 2.0 mm ID, 6μ) was used. The injection volume was 10 μL. The total run time per sample was 1.6 to 3.0 minutes. Tamoxifen and diclofenac were used as internal standards for the positive and negative mode, respectively. The percentage of parent drug compound remaining after each time point was determined relative to the initial measured concentration at the beginning of the reaction (T₀ min).

20 Data analysis:

[0457] For half-life determination, data was fitted using *GraphPad Prism, v 4.03* with the non-linear regression equation "one phase exponential decay" defined as:

$$Y = \text{Span} * \exp(-K * X) + \text{Plateau} \text{ (decays to Plateau with a first-order rate constant, K).}$$

"-K" is the slope of the curve. The half life (minutes), $T_{1/2} = \ln 0.6 / -K$ and is therefore defined as $-0.693 / -K$, or $0.693 / K$, a/k/a $-0.693 / \text{slope}$. Intrinsic Clearance (μl/min/mg protein) is defined as: $CL_{int} = 0.693 * (1 / T_{1/2}) * (\text{ml incubation/mg protein}) * 1000$; This equation can also be expressed as $(K * 1000) / \text{microsome conc.}$

Results:

[0458]

Table 3. Metabolic Stability Measured in Human Liver Microsomes:

Compound having formula	Half Life (minutes)	CL _{int} (μl/min/m g)		Half Life (minutes)	CL _{int} (μl/min/mg)
	Phase I only	Phase I only		Phase I + II	Phase I + II
I	Stable	< 1		348.9	2.0

[0459] The results had shown that *in vitro* half-life as determined from the microsomal assays demonstrated that compound of formula S-(I) under both phase I and phase I/II metabolic conditions. As shown in Table 3, the compound did not exhibit an intrinsic clearance (CL_{int}) value greater than 10 μl/min/mg. It is generally accepted that an *in vitro* CL_{int} value of less than 10 μl/min/mg protein represents favorable metabolic stability of the test compound. Compound of formula S-(I) exhibited low clearance in human liver microsomes. In conclusion, based on the data reported herein, compound of formula S-(I) exhibited favorable metabolic stability profiles *in vivo* studies.

EXAMPLE 7

Pharmacokinetics of Compound (I) in Dogs

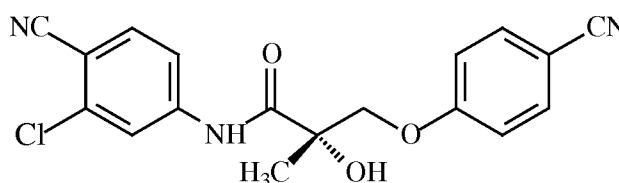
[0460] In order to determine the pharmacokinetics of the S-isomer of the Compound of formula (I), the compound was administered to beagle dogs perorally, and circulating plasma levels, terminal elimination half-life (t_{1/2}), total body clearance (CL), terminal volume distribution (V_z) and absolute bioavailability (F%) (Table 4) were determined. Compound S-(I) was rapidly and completely metabolized.

Table 4: **Pharmacokinetics in Dogs**

	Compound S-(I)
$t_{1/2}$ (h)	10.4 ± 0.5
CL (mL/min/kg)	1.68 ± 0.13
V _z (mL/kg)	1522 ± 142
F%	96.2%

Claims

1. A compound represented by the structure of formula S-(I)

**S-(I).**

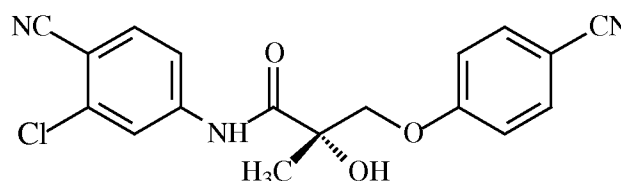
2. A composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier, diluent or salt, or a combination thereof.
3. A compound according to claim 1, or a composition according to claim 2, for use in contraception in a male subject; hormone therapy; treating a subject suffering from prostate cancer; delaying the progression of prostate cancer; treating a bone-related disorder, increasing a bone mass, promoting bone formation; treating, reducing the incidence of, delaying progression of, reducing the severity of, or alleviating symptoms associated with a muscle wasting disorder; treating, reducing the severity of, reducing the incidence of, delaying the onset of, or reducing pathogenesis of diabetes, glucose intolerance, hyperinsulinemia, insulin resistance, diseases associated with diabetes, fatty liver conditions, cardiovascular disease, cachexia; treating a disease or condition of the eye; reducing a fat mass; or increasing a lean mass.
4. A compound or a composition for use according to claim 3, wherein the bone-related disorder is selected from osteoporosis, osteopenia, increased bone resorption, bone fracture, bone frailty, loss of bone mineral density (BMD), or any combination thereof.
5. A compound or a composition for use according to claim 3 or 4, wherein the compound increases the strength of a bone, stimulates or enhances osteoblastogenesis, or inhibits osteoclast proliferation.
6. A compound or a composition for use according to claim 3, wherein said muscle wasting disorder is due to a pathology, illness, disease or condition.
7. A compound or a composition for use according to claim 6, wherein the pathology, illness, disease or condition is neurological, infectious, chronic or genetic.
8. A compound or a composition for use according to claim 6 or 7, wherein said pathology, illness, disease or condition is a muscular dystrophy, a muscular atrophy, X-linked spinal-bulbar muscular atrophy (SBMA), a cachexia, malnutrition, leprosy, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), cancer, end stage renal failure, sarcopenia, emphysema, osteomalacia, HIV infection, AIDS, or cardiomyopathy.
9. A compound or a composition for use according to claim 8, wherein said muscular dystrophy is Duchenne muscular dystrophy, Becker muscular dystrophy, or myotonic dystrophy.
10. A compound or a composition for use according to claim 3, wherein the muscle wasting disorder is an age-associated

muscle wasting disorder; a disuse deconditioning-associated muscle wasting disorder; or the muscle wasting disorder is due to chronic lower back pain; burns; central nervous system (CNS) injury or damage; peripheral nerve injury or damage; spinal cord injury or damage; chemical injury or damage; or alcoholism.

- 5 11. A compound or a composition for use according to claim 3, wherein the disease or condition of the eye comprises Sjögren's syndrome, or xerophthalmia.
12. A compound according to claim 1, or a composition according to claim 2, for use as a medicament.

10 Patentansprüche

1. Verbindung, dargestellt durch die Struktur der Formel S-(I)



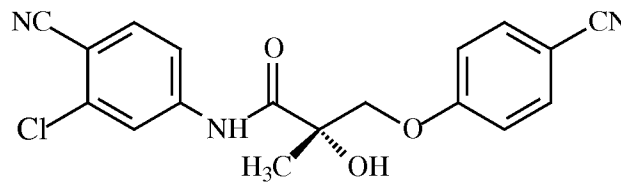
S- (I) .

- 25 2. Zusammensetzung, die eine Verbindung nach Anspruch 1 und einen pharmazeutisch verträglichen Träger, ein pharmazeutisch verträgliches Verdünnungsmittel oder Salz oder eine Kombination davon umfasst.
- 30 3. Verbindung nach Anspruch 1 oder einer Zusammensetzung nach Anspruch 2 zur Verwendung bei der Verhütung bei einem männlichen Subjekt; Hormontherapie; Behandeln eines Subjekts, das an Prostatakrebs leidet; Verzögern des Fortschreitens von Prostatakrebs; Behandeln einer knochenbezogenen Störung, Erhöhen einer Knochenmasse, Fördern der Knochenbildung; Behandeln von, Reduzieren der Inzidenz von, Verzögern des Fortschreitens von, Reduzieren der Schwere von oder Lindern von Symptomen im Zusammenhang mit einer Muskelschwundstörung; Behandeln von, Reduzieren der Schwere von, Reduzieren der Inzidenz von, Verzögern des Ausbruchs oder Reduzieren der Pathogenese von Diabetes, Glukoseintoleranz, Hyperinsulinämie, Insulinresistenz, Krankheiten im Zusammenhang mit Diabetes, Fettleberzustände, kardiovaskuläre Krankheit, Kachexie; Behandlung einer Krankheit oder eines Zustands des Auges; Reduzieren einer Fettmasse; oder Erhöhen einer Magermasse.
- 35 4. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3, wobei die knochenbezogene Störung aus Osteoporose, Osteopenie, erhöhter Knochenresorption, Knochenfraktur, Knochengebrechlichkeit, Verlust an Knochenmineraldichte (BMD) oder einer beliebigen Kombination davon ausgewählt ist.
- 40 5. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3 oder 4, wobei die Verbindung die Festigkeit eines Knochens erhöht, die Osteoblastengenese stimuliert oder verstärkt oder die Osteoklastenproliferation hemmt.
- 45 6. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3, wobei die Muskelschwundstörung auf eine Pathologie, eine Erkrankung, eine Krankheit oder einen Zustand zurückzuführen ist.
7. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 6, wobei die Pathologie, Erkrankung, Krankheit oder der Zustand neurologisch, infektiös, chronische oder genetisch ist.
- 50 8. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 6 oder 7, wobei die Pathologie, Erkrankung, Krankheit oder der Zustand eine Muskeldystrophie, eine Muskelatrophie, X-chromosomale spinal-bulbäre Muskelatrophie (SBMA), eine Kachexie, Unterernährung, Lepra, Diabetes, Nierenkrankheit, chronisch-obstruktive Lungenerkrankung (COPD), Krebs, Nierenversagen im Endstadium, Sarkopenie, Emphysem, Osteomalazie, HIV-Infektion, AIDS oder Kardiomyopathie ist.
- 55 9. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 8, wobei die Muskeldystrophie Duchenne-Muskeldystrophie, Becker-Muskeldystrophie oder myotonische Dystrophie ist.

10. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3, wobei die Muskelschwundstörung eine altersbedingte Muskelschwundstörung; eine mit Inaktivierungsdekonditionierung in Zusammenhang stehende Muskelschwundstörung; oder die Muskelschwundstörung auf chronische Schmerzen im unteren Rücken; Verbrennungen; Zentralnervensystem (ZNS)-Verletzung oder -Schädigung; Verletzung oder Schädigung peripherer Nerven; Rückenmarksverletzung oder -Schädigung; chemische Verletzung oder Schädigung; oder Alkoholismus zurückzuführen ist.
11. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3, wobei die Krankheit oder der Zustand des Auges Sjögren-Syndrom oder Xerophthalmie umfasst.
12. Verbindung nach Anspruch 1 oder Zusammensetzung nach Anspruch 2 zur Verwendung als Medikament.

Revendications

1. Composé représenté par la structure de formule S-(I)



S-(I).

2. Composition comprenant un composé selon la revendication 1, et un véhicule, diluant ou sel acceptable sur le plan pharmaceutique, ou une de leurs combinaisons.
3. Composé selon la revendication 1, ou composition selon la revendication 2, destiné à être utilisé pour la contraception chez un sujet mâle ; une thérapie aux hormones ; traiter un sujet souffrant du cancer de la prostate ; retarder la progression du cancer de la prostate ; traiter un trouble lié aux os, l'augmentation d'une masse osseuse, la promotion de formation osseuse ; traiter, réduire l'incidence de, retarder la progression de, réduire la gravité de ou atténuer les symptômes associés à un trouble d'affaiblissement musculaire ; traiter, réduire la gravité, réduire l'incidence, retarder l'apparition ou réduire la pathogenèse d'un diabète, d'une intolérance au glucose, d'une hyperinsulinémie, d'une résistance à l'insuline, de maladies associées au diabète, d'affections de stéatose hépatique, d'une maladie cardiovasculaire, d'une cachexie ; traiter une maladie ou une affection de l'oeil ; réduire une masse grasseuse ; ou augmenter une masse maigre.
4. Composé ou composition utilisable selon la revendication 3, dans lequel le trouble lié aux os est choisi parmi l'ostéoporose, l'ostéopénie, une résorption osseuse accrue, une fracture osseuse, une fragilité osseuse, une perte de densité minérale osseuse (DMO), ou n'importe quelle combinaison de ceux-ci.
5. Composé ou composition utilisable selon la revendication 3 ou 4, dans lequel le composé augmente la solidité d'un os, stimule ou renforce l'ostéoblastogenèse, ou inhibe la prolifération d'ostéoclastes.
6. Composé ou composition utilisable selon la revendication 3, dans lequel ledit trouble d'affaiblissement musculaire est dû à une pathologie, une maladie ou une affection.
7. Composé ou composition utilisable selon la revendication 6, dans lequel la pathologie, la maladie ou l'affection est neurologique, infectieuse, chronique ou génétique.
8. Composé ou composition utilisable selon la revendication 6 ou 7, dans lequel ladite pathologie, maladie ou affection est une dystrophie musculaire, une amyotrophie, une amyotrophie bulbospinale liée à l'X (ABS-X), une cachexie, une malnutrition, la lèpre, un diabète, une maladie rénale, une maladie pulmonaire obstructive chronique (MPOC), un cancer, une insuffisance rénale terminale, une sarcopénie, un emphysème, une ostéomalacie, une infection au VIH, un SIDA ou une cardiomyopathie.

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9. Composé ou composition utilisable selon la revendication 8, dans lequel ladite dystrophie musculaire est la dystrophie musculaire de Duchenne, la dystrophie musculaire de Becker ou la dystrophie myotonique.

5 10. Composé ou composition utilisable selon la revendication 3, dans lequel le trouble d'affaiblissement musculaire est un trouble d'affaiblissement musculaire associé à l'âge ; un trouble d'affaiblissement musculaire associé à un déconditionnement d'inactivité ; ou ledit trouble d'affaiblissement musculaire est dû à des lombalgies chroniques ; des brûlures ; un traumatisme ou une lésion du système nerveux central (CNS) ; un traumatisme ou une lésion de nerfs périphériques ; un traumatisme ou une lésion de la moelle épinière ; un traumatisme ou une lésion chimique ; ou l'alcoolisme.

10 11. Composé ou composition utilisable selon la revendication 3, où la maladie ou affection de l'oeil comprend le syndrome de Sjögren ou la xérophtalmie.

15 12. Composé selon la revendication 1, ou composition selon la revendication 2, pour une utilisation en tant que médicament.

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Figure 1A

I. Synthesis process for (S)-I :

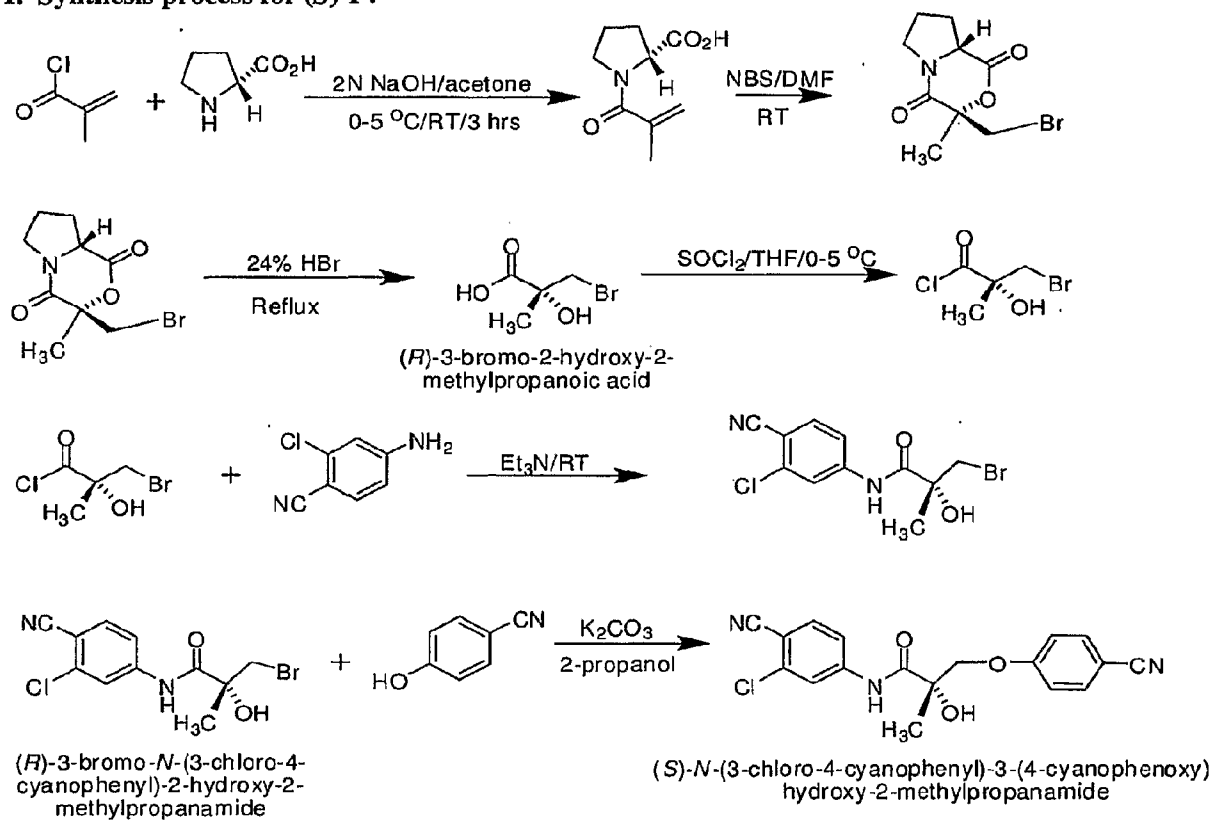


Figure 1B

II. Synthesis process for (R)-I :

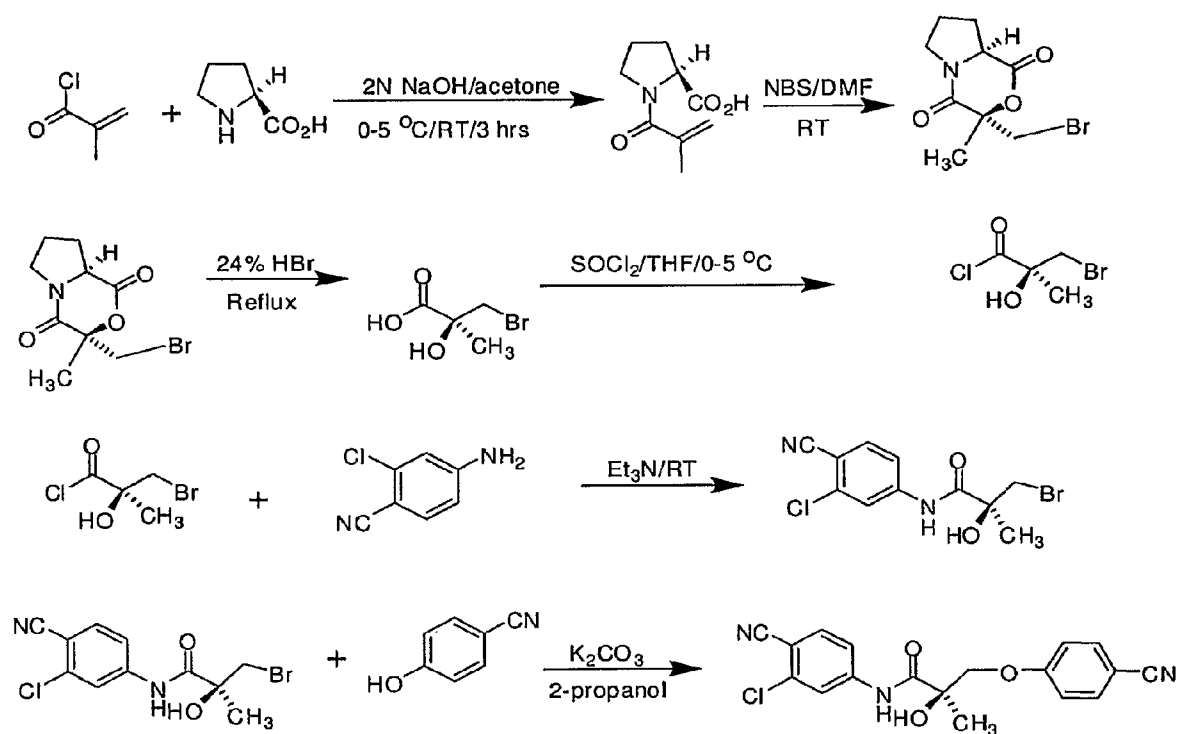


Figure 1C

III. Synthetic process for (S)-I (oxirane intermediate):

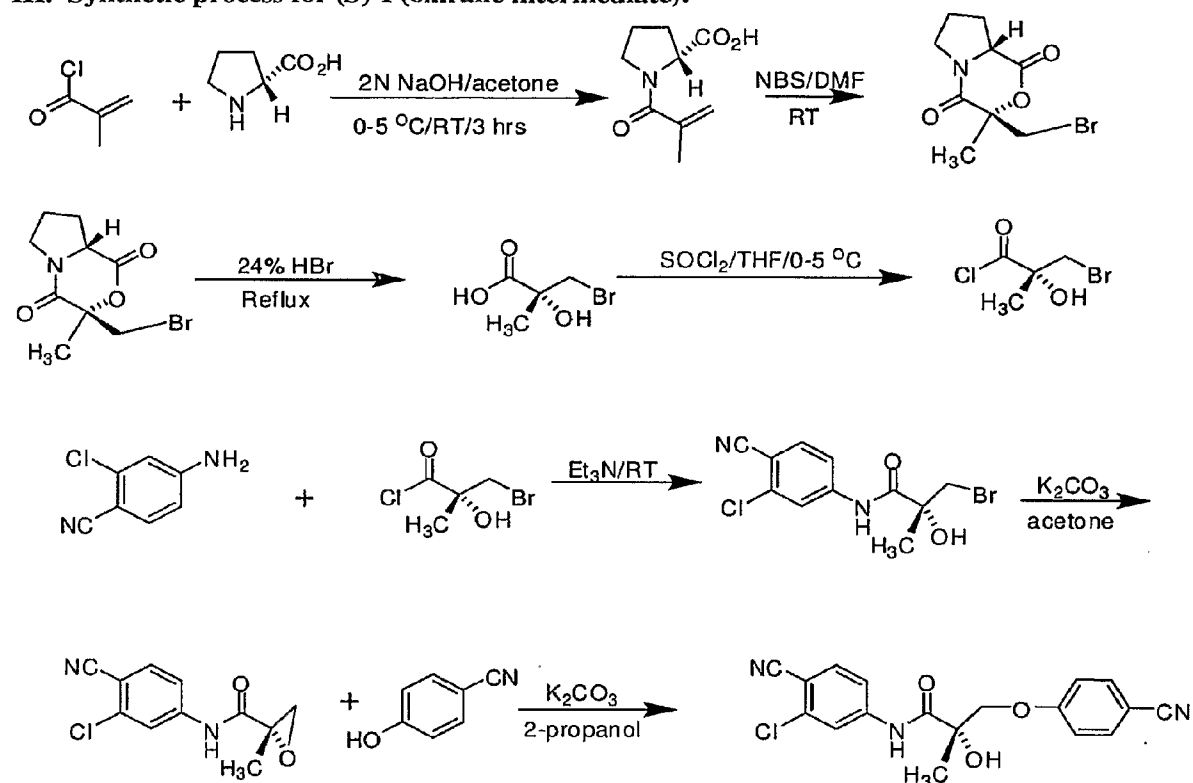


Figure 1D

IV. Synthetic process for (R)-I (oxirane intermediate):

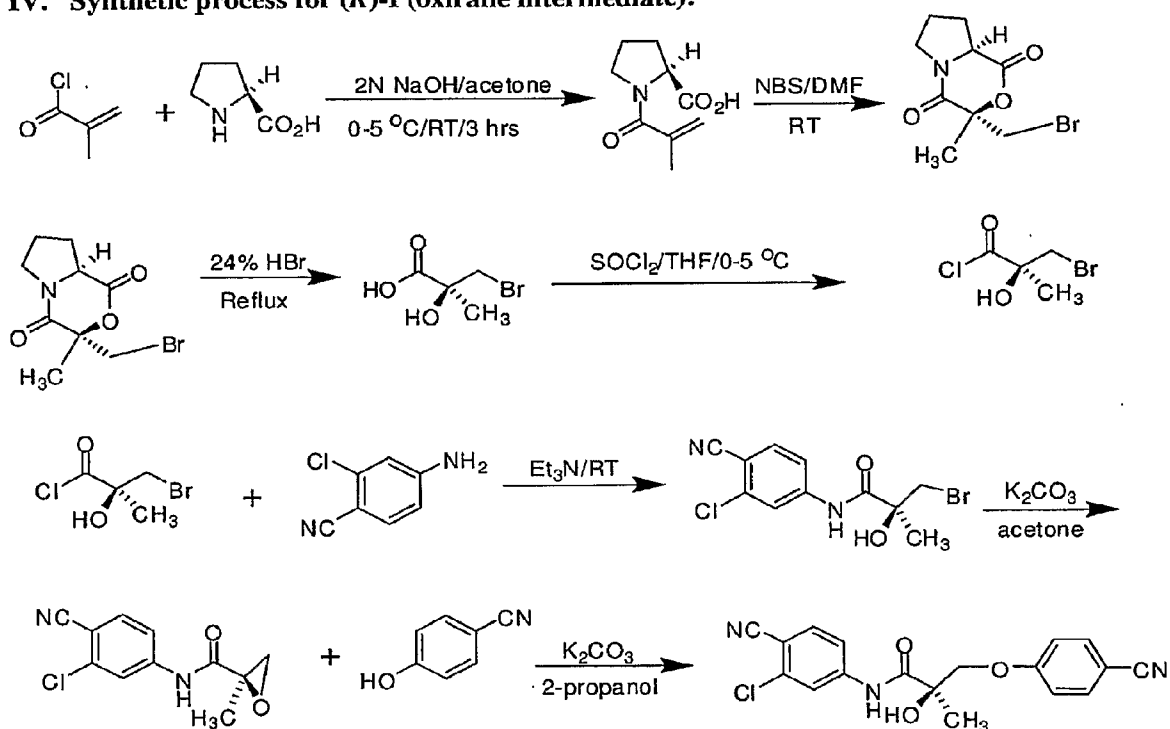


Figure 1E

V. Synthetic process for (S)-I involving B-ring addition prior to A-ring addition:

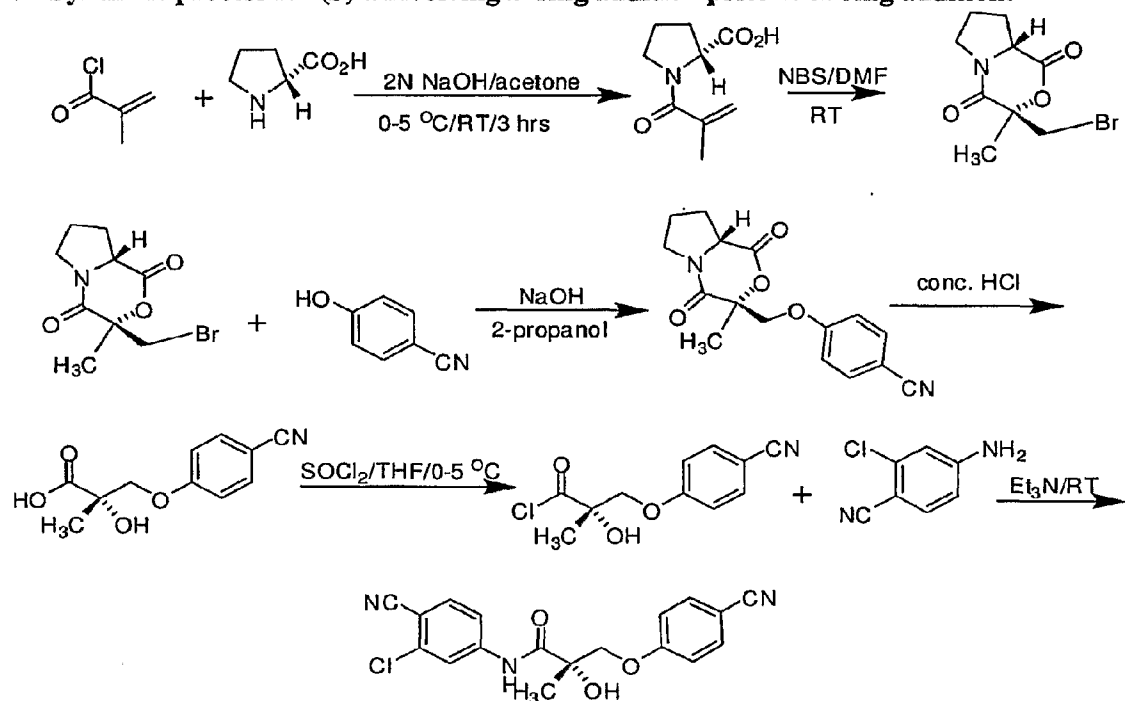


Figure 1F

VI. Synthetic process for (R)-I involving B-ring addition prior to A-ring addition:

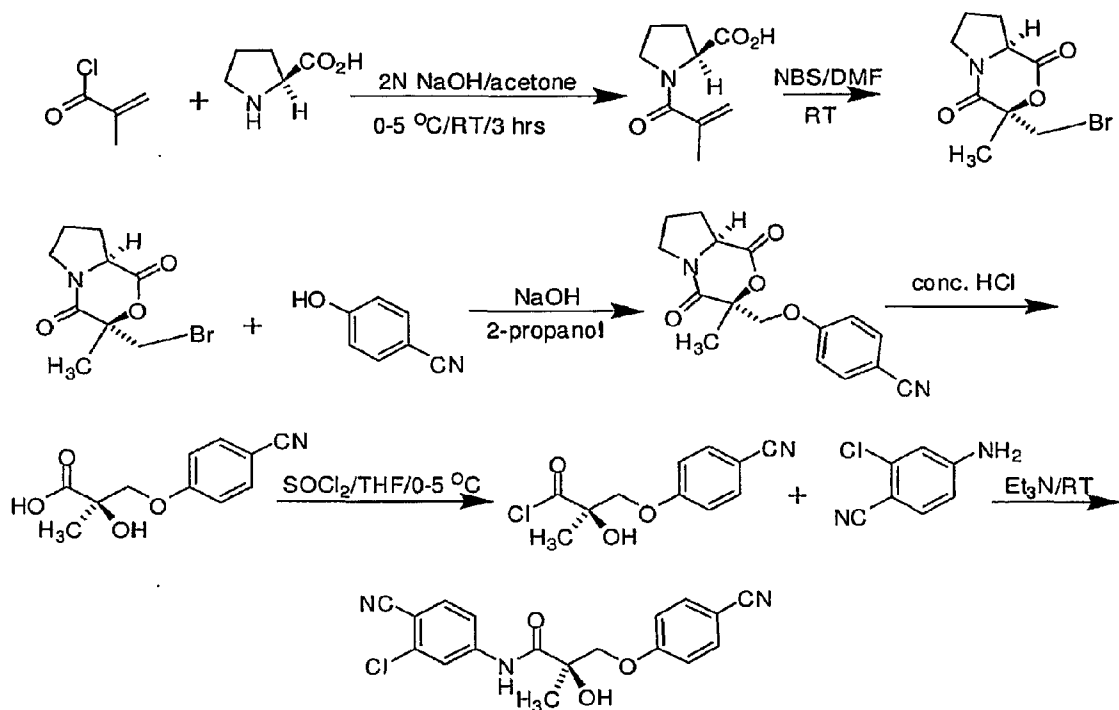


Figure 1G

VII. Synthetic process for (S)-I using chiral intermediate and involving B-ring addition prior to A-ring addition:

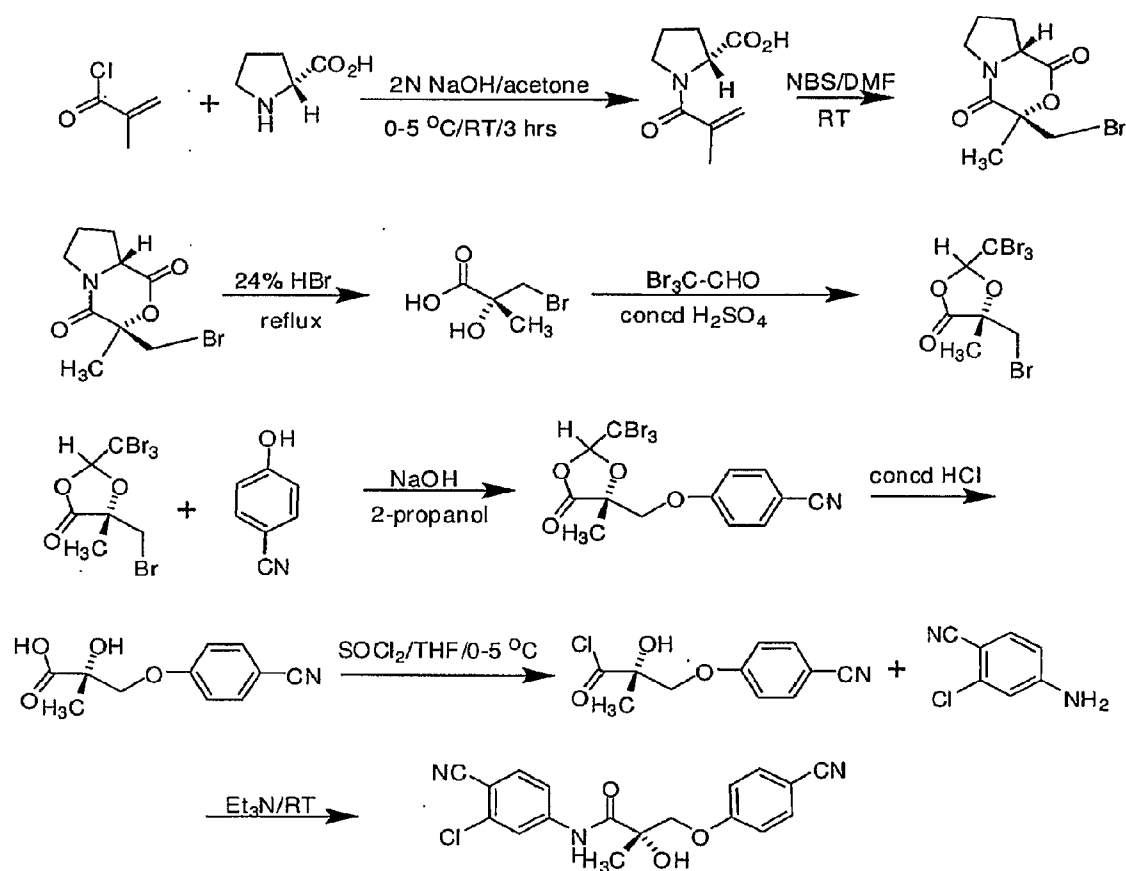


Figure 1H

VIII. Synthetic process for (R)-I using chiral intermediate and involving B-ring addition prior to A-ring addition:

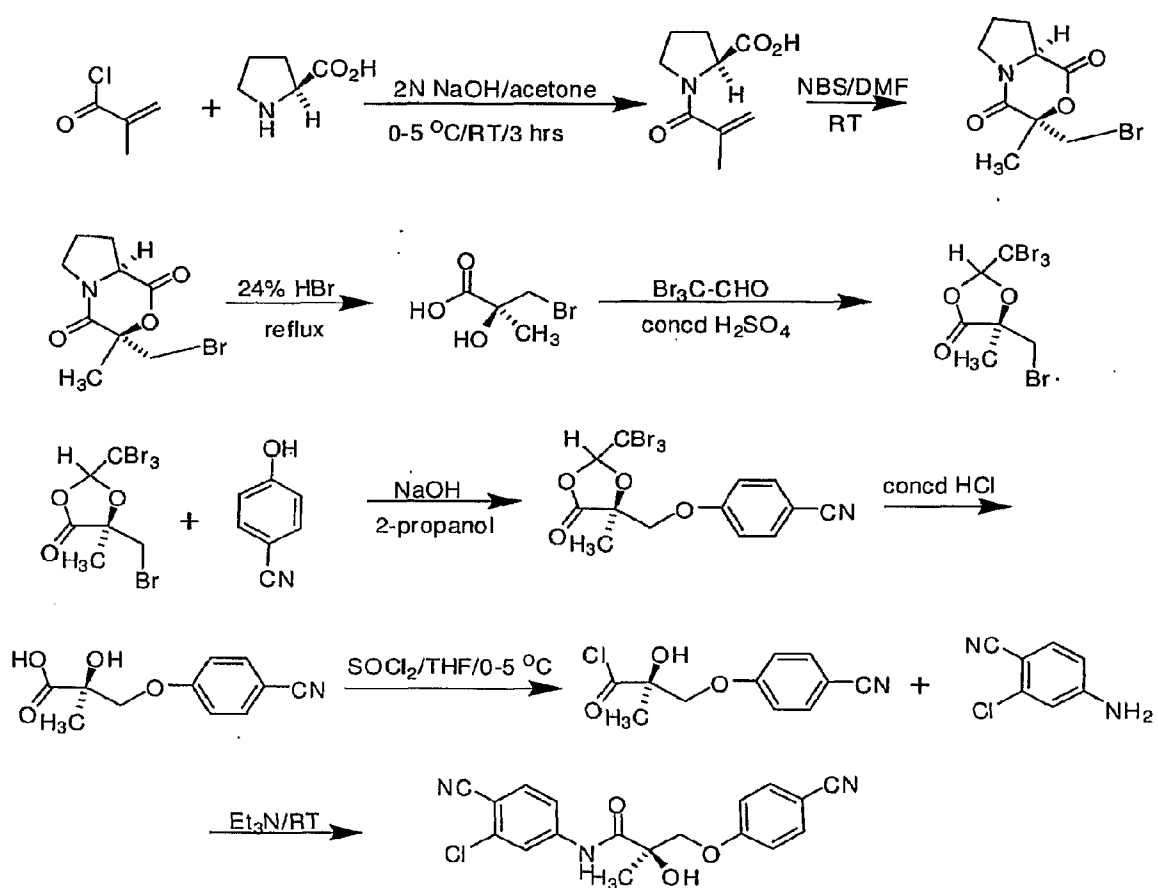


Figure 11

IX. Racemic synthetic process for compound I involving oxazolidinedione intermediate:

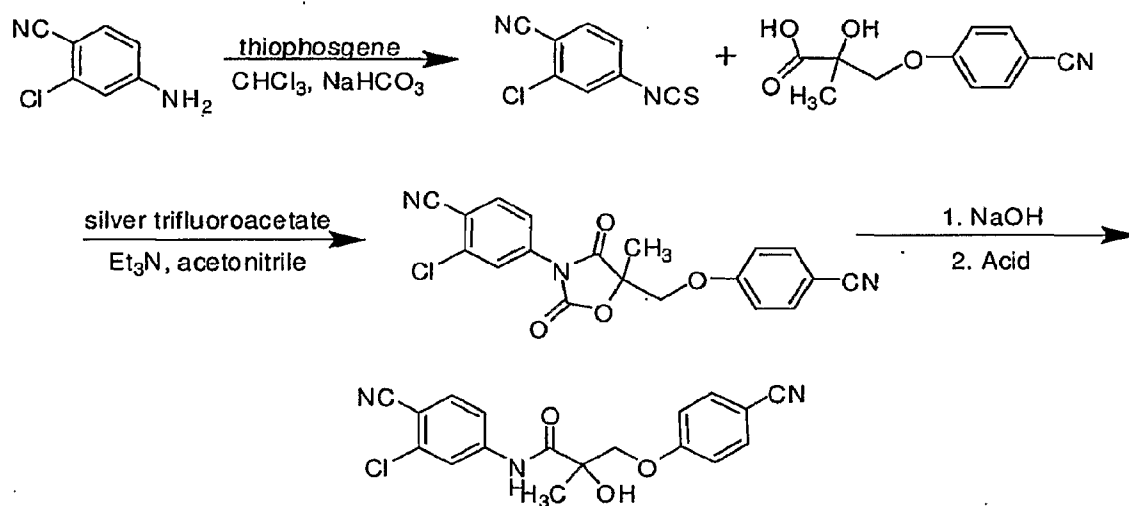


Figure 1J

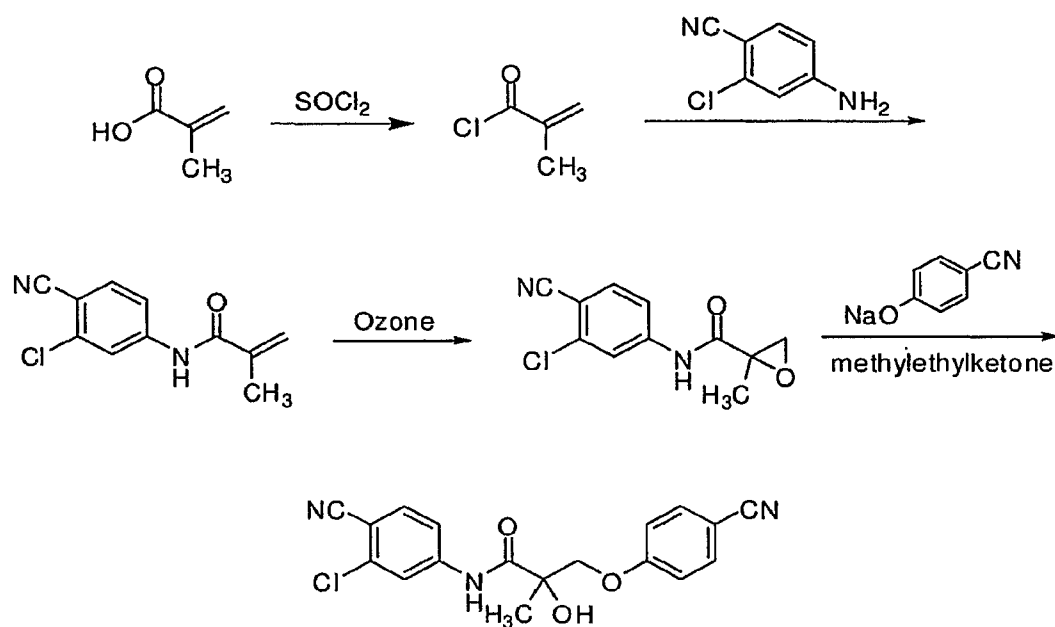
X. Racemic synthetic process for compound I involving oxirane intermediate:

Figure 1K

XI. Large-scale synthetic process for (S)-I:

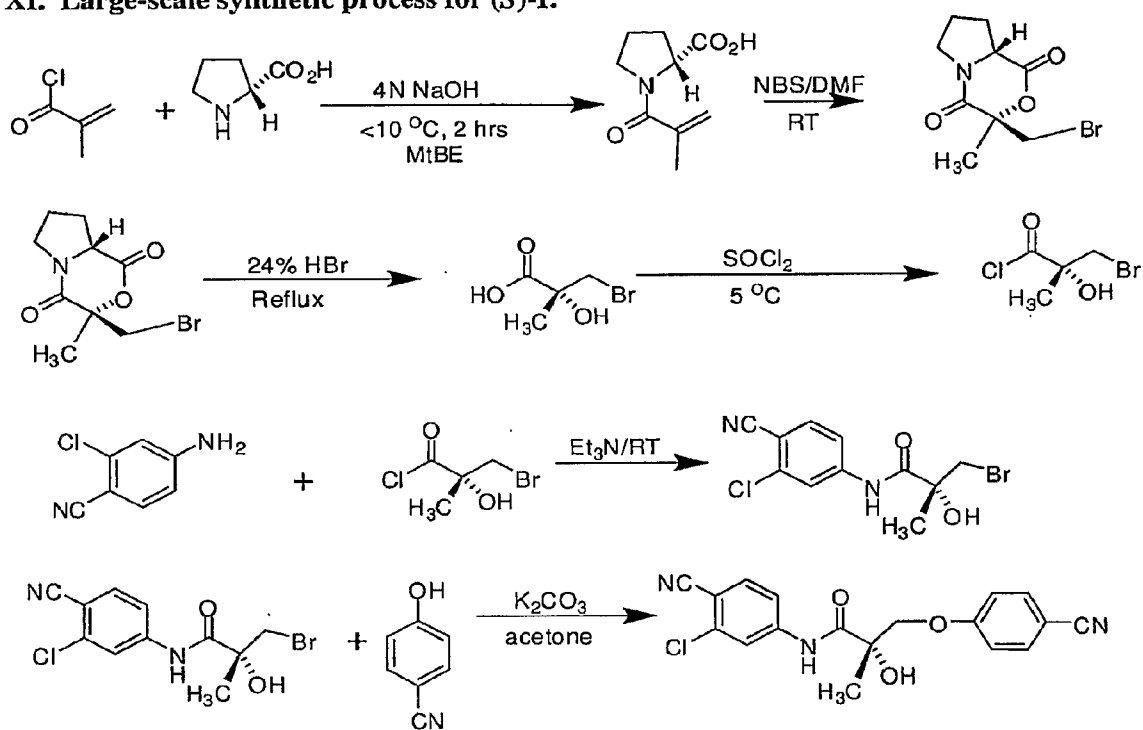
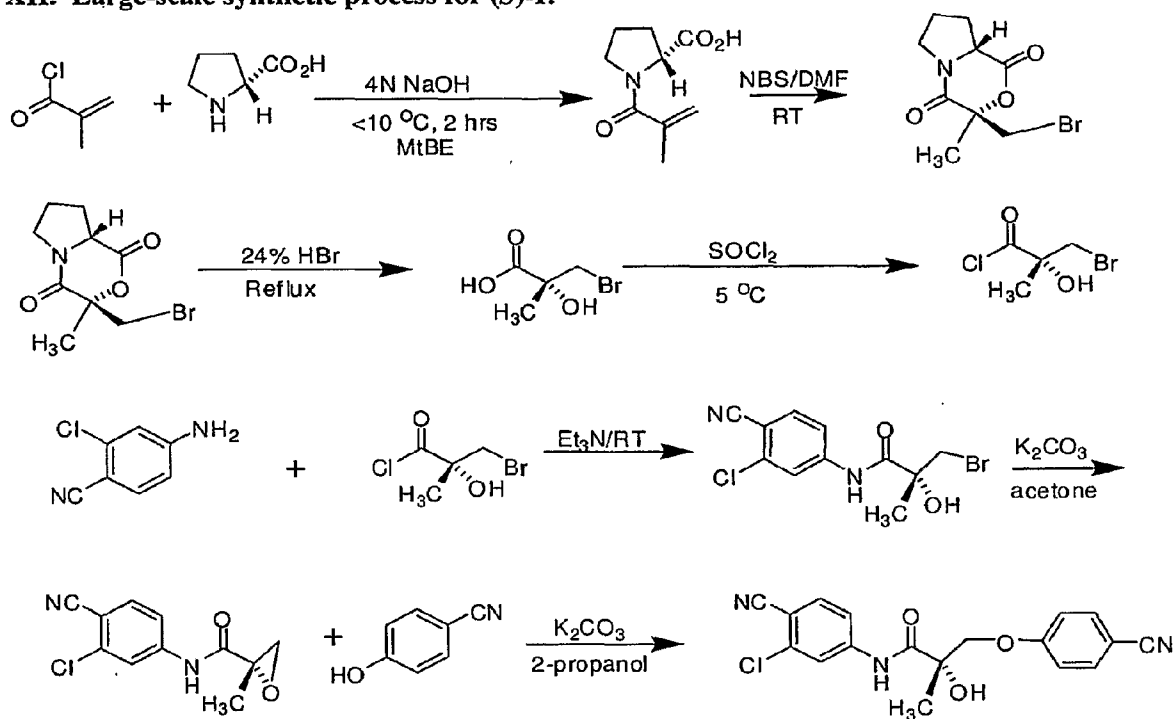


Figure 1L

XII. Large-scale synthetic process for (S)-I:



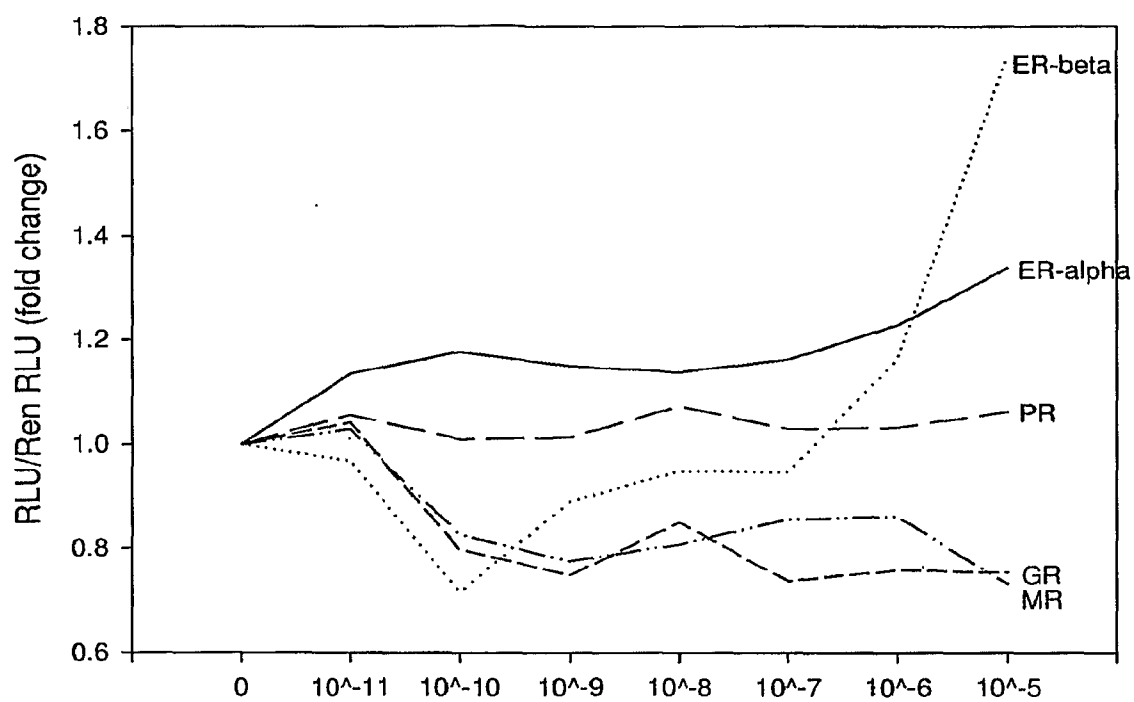


FIGURE 2

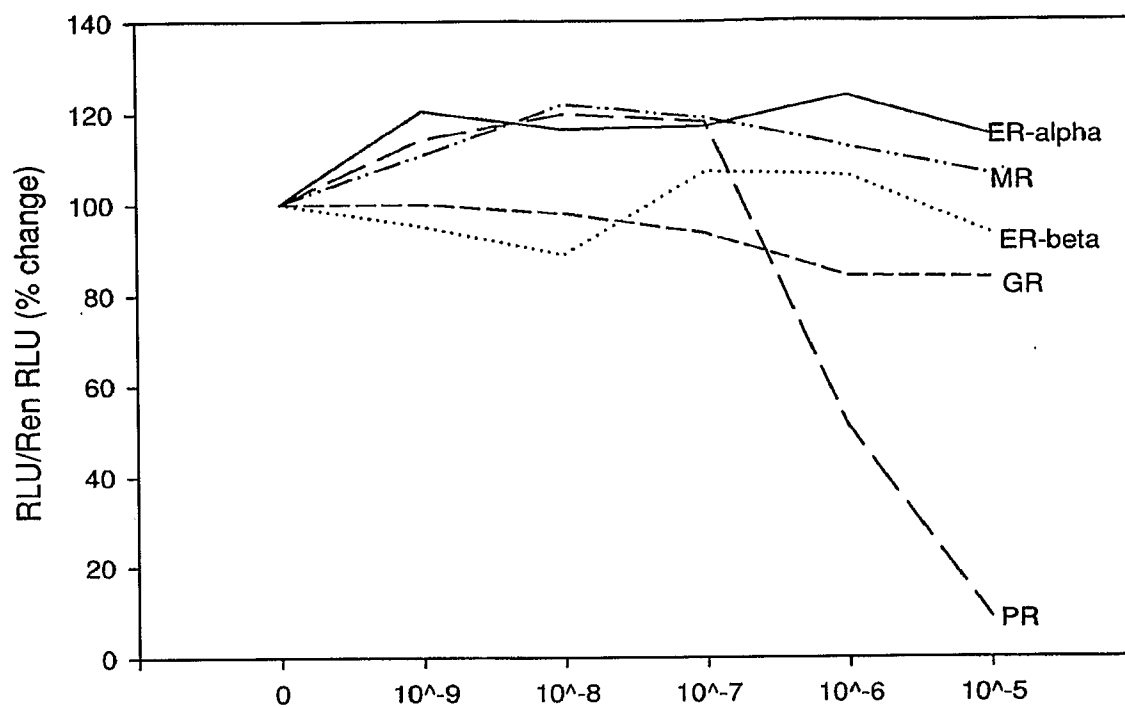


FIGURE 3

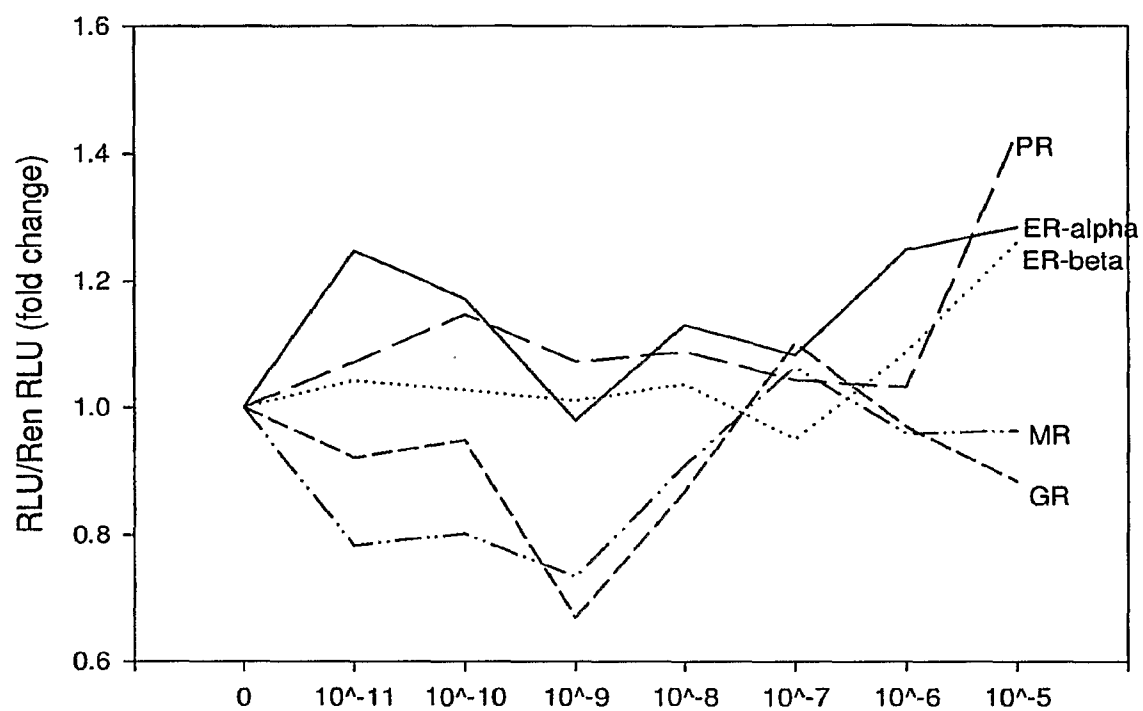


FIGURE 4

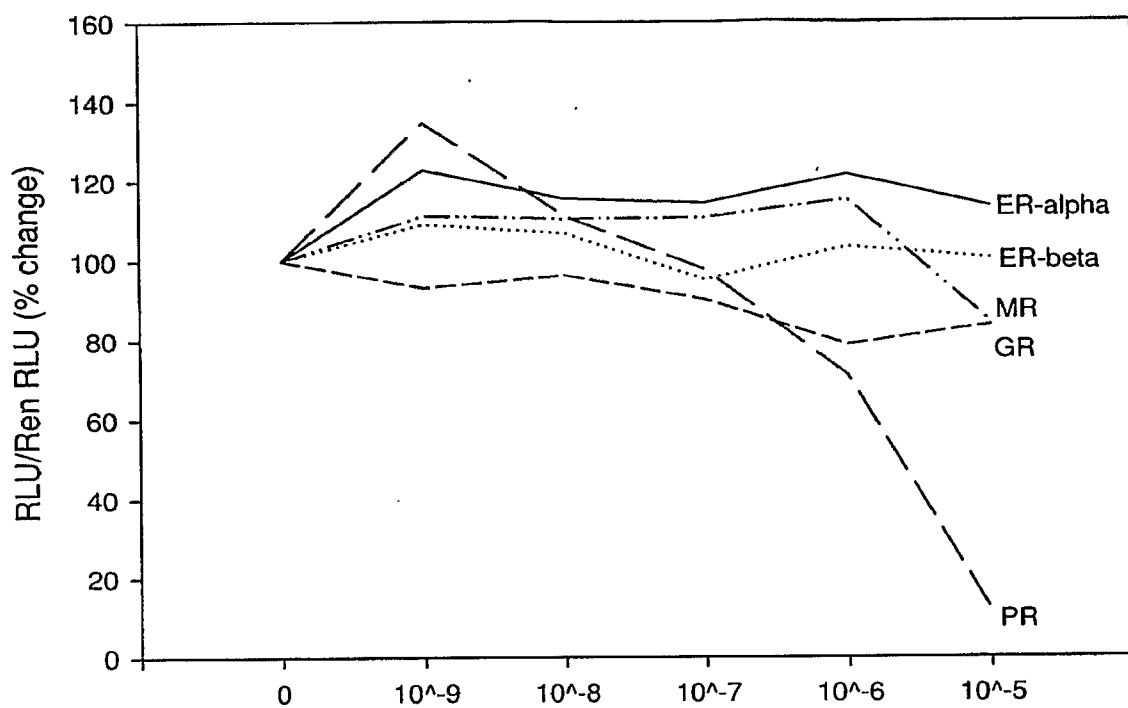


FIGURE 5

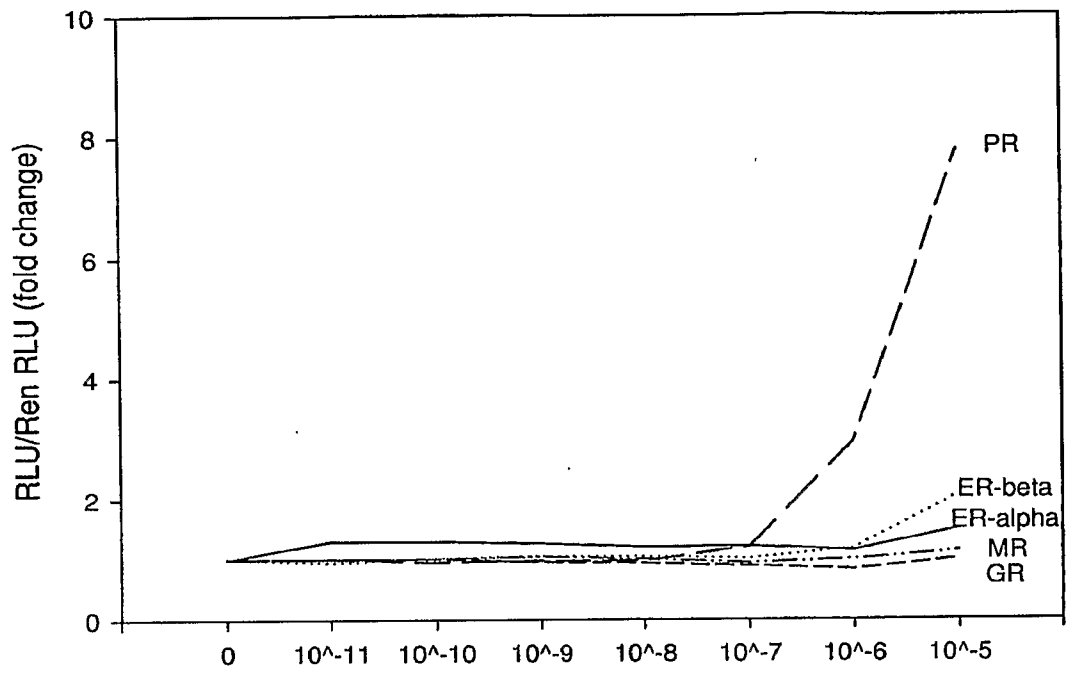


FIGURE 6

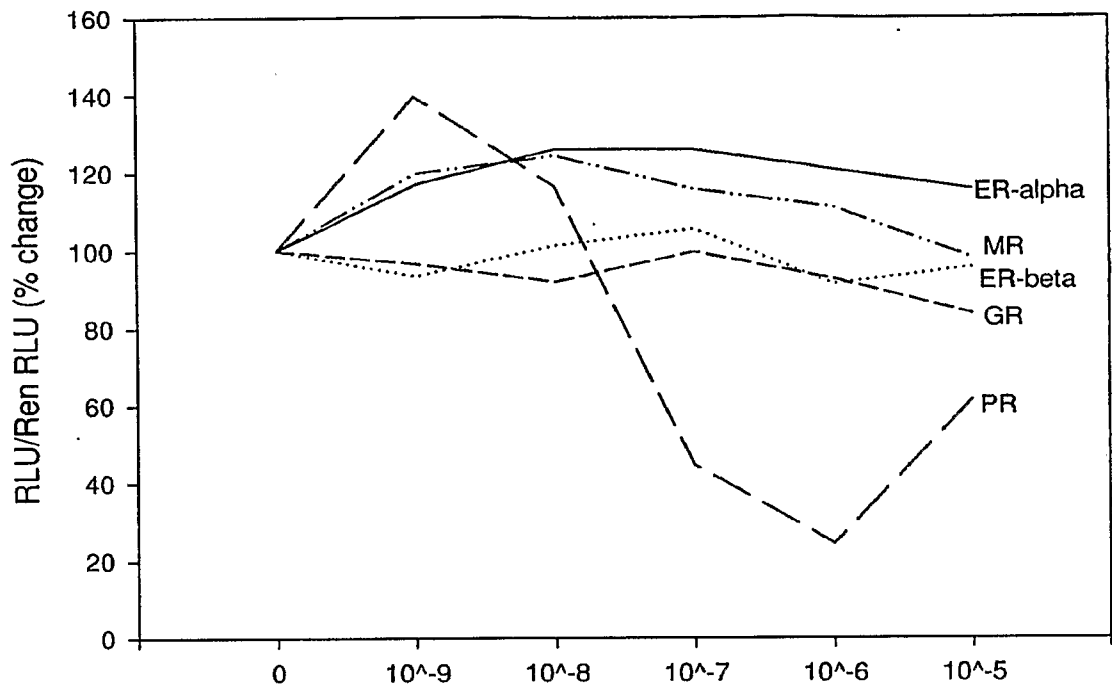


FIGURE 7

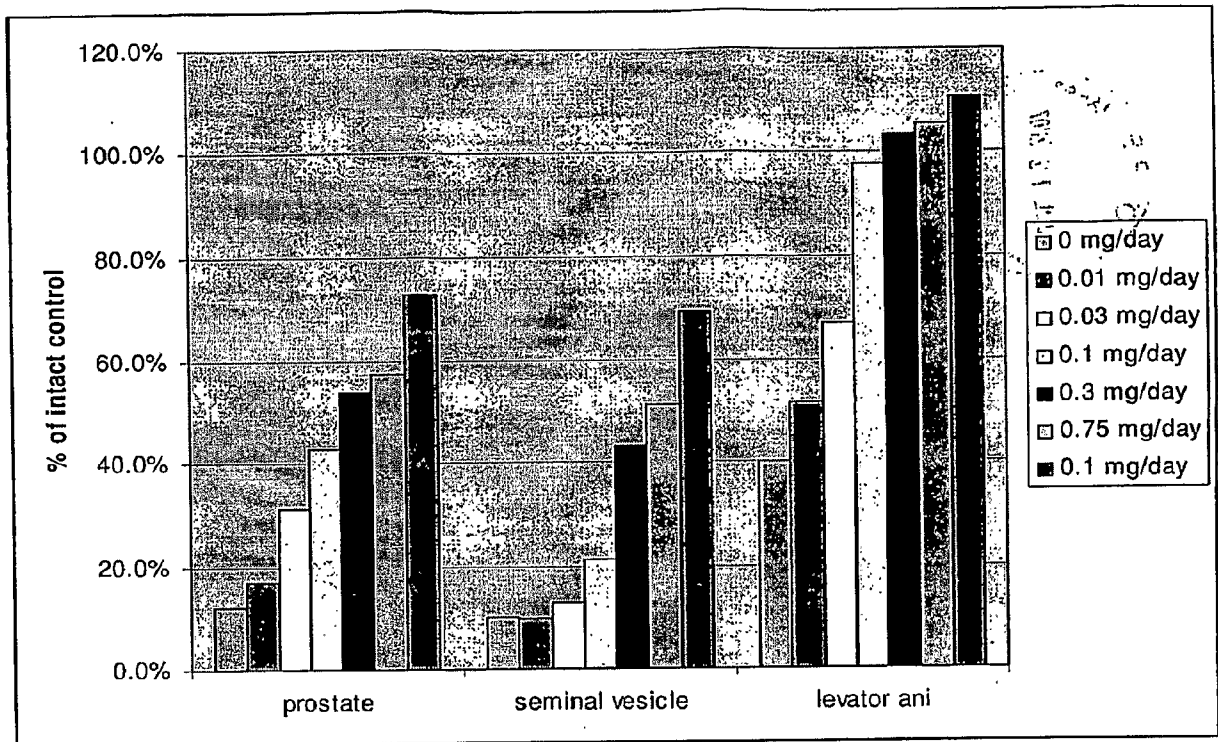


FIGURE 8

REFERENCES CITED IN THE DESCRIPTION

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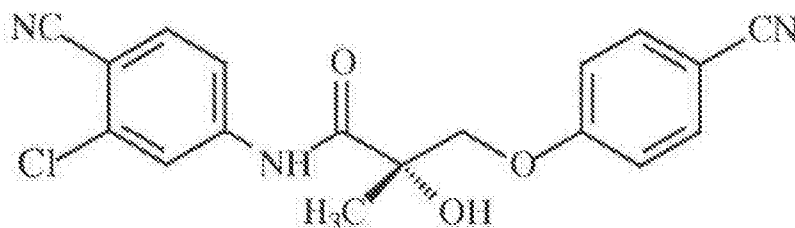
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Szubstituíált acetanilidek és azok alkalmazási módszerei

Szabadalmi igénypontok



1. Egy *S*-(I):



S-(I).

szerkezetű vegyület.

2. Készítmény, mely egy 1. igénypont szerinti vegyületet és egy gyógyászatilag elfogadható hordozót, hígítószeret vagy só, vagy azok kombinációját tartalmazza.

3. Az 1. igénypont szerinti vegyület vagy a 2. igénypont szerinti készítmény felnőtt alany fogamzásgátlásában; hormonterápiában; prosztatárákban szenvedő alany kezelésében; prosztatárák kifejlődésének késleltetésében; csonttal kapcsolatos betegség kezelésében, csonttömeg növelésében, csontképződés elősegítésében; izomsorvadásos betegségek kezelésében, gyakoriságának csökkentésében, kifejlődésének késleltetésében, súlyosságának mérséklésében vagy azzal összefüggő tünetek enyhítésében; diabetes, glükóz intolerancia, hyperinsulinemia, inzulinrezisztencia, diabétessel összefüggő betegségek, máj steatosis, szív- és érrendszeri betegségek, cachexia kezelésében, súlyosságának mérséklésében, gyakoriságának csökkentésében, kifejlődésének késleltetésében, vagy patogenézisének mérséklésében; szem betegség vagy a szem állapotának kezelésében; zsírtömeg csökkentésében; vagy sovány-ság tömegének növelésében történő alkalmazásra.

4. Vegyület vagy készítmény a 3. igénypont szerinti alkalmazásra, ahol a csonttal kapcsolatos betegség osteoporosis, osteopenia, fokozott csont reszorpció, csonttörés, csonttörékenység, csont ásványi anyagtartalom vesztes (BMD), vagy ezek bármely kombinációja közül kerül ki.

5. Vegyület vagy készítmény a 3. vagy 4. igénypont szerinti alkalmazásra, ahol a vegyület növeli a csont erősségét, stimulálja és fokozza az osteoblastogenezist, vagy gátolja az osteoclast proliferációt.
6. Vegyület vagy készítmény a 3. igénypont szerinti alkalmazásra, ahol az izomsorvadásos betegség patológiás állapot, betegség, kór vagy állapot következménye.
7. Vegyület vagy készítmény a 6. igénypont szerinti alkalmazásra, ahol a patológiás állapot, betegség, kór vagy állapot neurológiai, fertőzőes, krónikus vagy genetikai.
8. Vegyület vagy készítmény a 6. vagy 7. igénypont szerinti alkalmazásra, ahol a patológiás állapot, betegség, kór vagy állapot izom dystrophia, izom atrophia, X-kromoszómához köthető gerinc-bulbaris izom atrophia (SBMA), egy cachexia, alultápláltság, lepra, diabetes, vesebetegség, krónikus elzáródásos tüdőbetegség (COPD), rák, végső stádiumú veseelégtelenség, sarcopenia, emphysema, osteomalacia, HIV fertőzés, AIDS, vagy cardiomyopathia.
9. Vegyület vagy készítmény a 8. igénypont szerinti alkalmazásra, ahol az izom dystrophia Duchenne izom dystrophia, Becker izom dystrophia, vagy myotoniás dystrophia.
10. Vegyület vagy készítmény a 3. igénypont szerinti alkalmazásra, ahol az izomsorvadásos betegség egy korrrel járó betegség; egy használat hiánya miatti kondíciórömlással összefüggő izomsorvadásos betegség; vagy az izomsorvadás krónikus derékfájdalom; égések; központi idegrendszer (CNS) sérülés vagy károsodás; perifériás idegrendszer sérülés vagy károsodás; gerincvelő sérülés vagy károsodás; kémiai sérülés vagy károsodás; vagy alkoholizmus következménye.
11. Vegyület vagy készítmény a 3. igénypont szerinti alkalmazásra, ahol szem betegség vagy a szem állapota Sjögren-szindróma vagy xerophthalmia.
12. Az 1. igénypont szerinti vegyület vagy egy 2. igénypont szerinti készítmény gyógyszerként történő alkalmazásra.

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