(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/106401 A1

(51) International Patent Classification[7]: C07C 233/05, C07D 211/72, 239/02, 233/44, A61K 31/65, 31/44, 31/505, 31/415

(21) International Application Number: PCT/US03/16219

(22) International Filing Date: 17 June 2003 (17.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/388,739 17 June 2002 (17.06.2002) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF TENNESSEE RESEARCH FOUNDATION** [US/US]; 1534 White Avenue, Suite 403, Knoxville, TN 37996-1527 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DALTON, James** [US/US]; 2706 Wellesley Drive, Upper Arlington, OH 43221 (US). **MILLER, Duane, D.** [US/US]; 8706 Maple Creek Cove, Germantown, TN 38139 (US). **MARHEFKA, Craig, A.** [US/US]; 99 Lewis Road, Belmont, MA 02478 (US). **GAO, Wenqing** [CN/US]; 991 Manor Lane, Apt. F., Columbus, OH 43221 (US).

(74) Agent: **COHEN, Mark, S.**; Eitan, Pearl, Latzer & Cohen-Zedek, L.L.P., 10 Rockefeller Plaza, Suite 1001, New York, NY 10020 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: N-BRIDGED SELECTIVE ANDROGEN RECEPTOR MODULATORS AND METHODS OF USE THEREOF

(57) Abstract: This invention provides a class of androgen receptor targeting agents (ARTA) The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). Several of the SARM compounds have been found to have an unexpected androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. Other SARM compounds have been found to have an unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. The SARM compounds, either alone or as a composition, 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 Decline in 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 acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy, and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

WO 03/106401 A1

N-BRIDGED SELECTIVE ANDROGEN RECEPTOR MODULATORS AND METHODS OF USE THEREOF

FIELD OF INVENTION

[0001] The present invention relates to a novel class of androgen receptor targeting agents (ARTA), which demonstrate androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARMs) 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); c) treatment of conditions associated with Androgen Decline in Female (ADIF); d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

BACKGROUND OF THE INVENTION

[0002] 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) ("Sundaram")). 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.

[0003] 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.

[0004] 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)).

[0005] 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)).

[0006] Steroidal ligands which bind the AR and act as androgens (e.g. testosterone enanthate) or as antiandrogens (e.g. cyproterone acetate) have been known for many years and are used clinically (Wu 1988). Although nonsteroidal antiandrogens are in clinical use for hormone-dependent prostate cancer, nonsteroidal androgens have not been reported. For this reason, research on male contraceptives has focused solely on steroidal compounds.

[0007] Prostate cancer is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Unfortunately, over sixty percent of newly diagnosed cases of prostate cancer are found

to be pathologically advanced, with no cure and a dismal prognosis. One approach to this problem is to find prostate cancer earlier through screening programs and thereby reduce the number of advanced prostate cancer patients. Another strategy, however, is to develop drugs to prevent prostate cancer. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer. Thus, the development of treatment and preventative strategies against prostate cancer may have the greatest overall impact both medically and economically against prostate cancer.

[0008] 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.

[0009] 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.

[00010] Androgen decline in the aging male (ADAM) refers to a progressive decrease in androgen production, common in males after middle age. The syndrome is characterized by alterations in the physical and intellectual domains that correlate with and can be corrected by manipulation of the androgen milieu. ADAM is characterized biochemically by a decrease not only in serum androgen, but also in other hormones, such as growth hormone, melatonin and dehydroepiandrosterone. Clinical manifestations include fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, anemia, alterations in mood and cognition and prostate cancer.

[00011]Androgen Deficiency in Female (ADIF) refers to a variety of hormone-related conditions including, common in females after middle agest. The syndrome is characterized by sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, anemia, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer.

[00012]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. The loss of muscle mass that

occurs during muscle wasting can be characterized by a muscle protein breakdown or degradation. Protein degradation occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Protein degradation, 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. 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, Emphysema, Osteomalacia, HIV Infection, AIDS, and Cardiomyopathy, 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. 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 infection, poor performance status and susceptibility to injury.

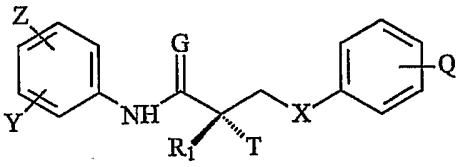
[00013]New innovative approaches are urgently needed at both the basic science and clinical levels to develop compounds which are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such 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 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 acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

SUMMARY OF THE INVENTION

[00014]In one embodiment, this invention provides a class of androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). Several of the SARM compounds have been found to have an unexpected androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. Other SARM compounds have been found to have an unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. The SARM compounds, either alone or as a composition, 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 Decline in 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 acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

[00015]In one embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein G is O or S;

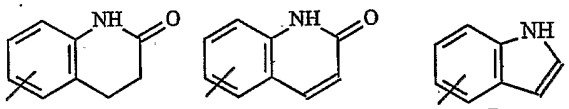
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



A B C

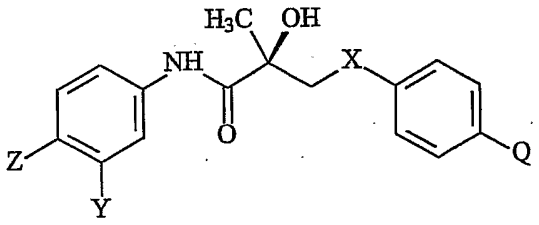
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3.

[00016] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula I, or any combination thereof.

[00017] In one embodiment, X in formula I is NH. In another embodiment, T in formula I is OH. In another embodiment, R_1 in formula I is CH_3. In another embodiment, G in formula I is O. In another embodiment, Z in formula I is NO_2. In another embodiment, Z in formula I is CN. In another embodiment, Y in formula I is CF_3. In another embodiment, Q in formula I is $NHCOCH_3$. In another embodiment, Q in formula I is F.

[00018]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



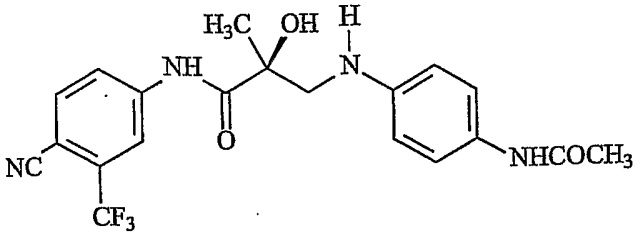
II

wherein Z, Y, X and Q are as defined above for compound I.

[00019]In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II, or any combination thereof.

[00020]In one embodiment, X in formula II is NH. In another embodiment, Z in formula II is NO_2. In another embodiment, Z in formula II is CN. In another embodiment, Y in formula II is CF_3. In another embodiment, Q in formula II is $NHCOCH_3$. In another embodiment, Q in formula II is F.

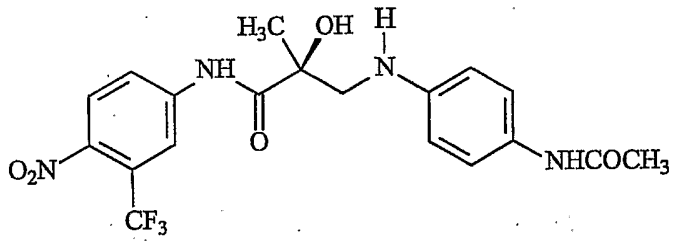
[00021]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



III

[00022] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula III, or any combination thereof.

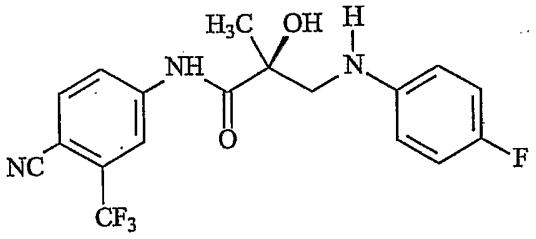
[00023] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

[00024] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV, or any combination thereof.

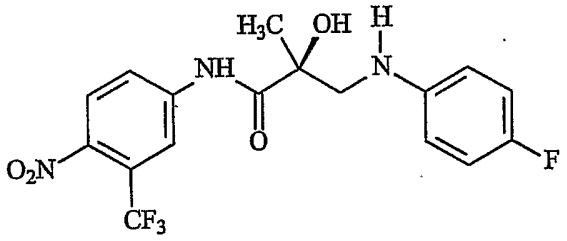
[00025] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula V:



V

[00026] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula V, or any combination thereof.

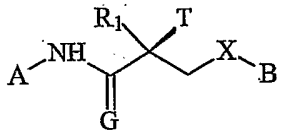
[00027]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VI:



VI

[00028] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VI, or any combination thereof.

[00029]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VII:



VII

wherein G is O or S;

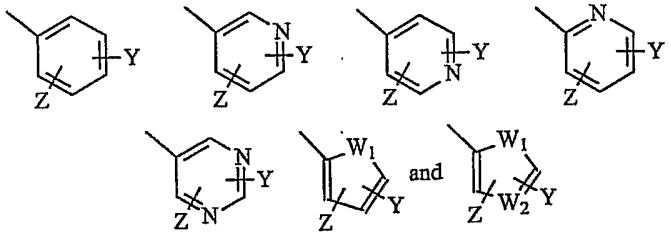
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

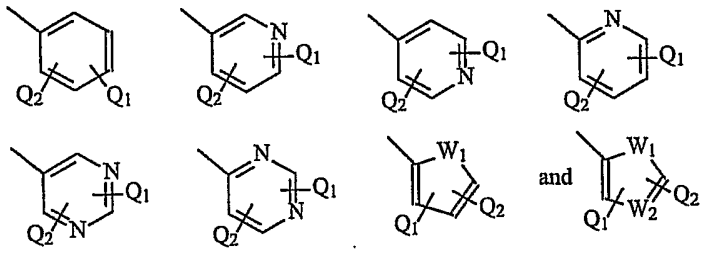
R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:

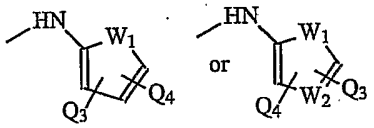


wherein A and B cannot simultaneously be a benzene ring;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 and Q_2 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO,



Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN or NCO;

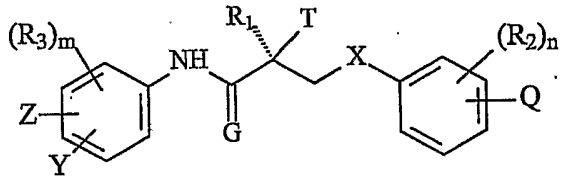
W_1 is O, NH, NR, NO or S; and

W_2 is N or NO.

[00030] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VII, or any combination thereof.

[00031]In one embodiment, X in formula VII is NH. In another embodiment, T in formula VII is OH. In another embodiment, R_1 in formula VII is CH_3. In another embodiment, G in formula VII is O. In another embodiment, Z in formula VII is NO_2. In another embodiment, Z in formula VII is CN. In another embodiment, Y in formula VIII is CF_3. In another embodiment, Q_1 in formula VII is $NHCOCH_3$. In another embodiment, Q_1 in formula VII is F.

[00032]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VIII:



VIII

wherein X is NH, NO or NR;

G is O or S;

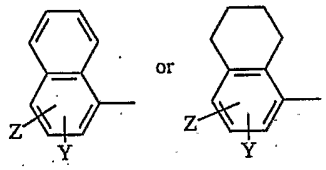
T is OH, OR, -NHCOCH$_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH$_2$F, CHF$_2$, CF$_3$, CF$_2$CF$_3$, aryl, phenyl, halogen, alkenyl or OH;

R$_1$ is CH$_3$, CH$_2$F, CHF$_2$, CF$_3$, CH$_2$CH$_3$, or CF$_2$CF$_3$;

R$_2$ is F, Cl, Br, I, CH$_3$, CF$_3$, OH, CN, NO$_2$, NHCOCH$_3$, NHCOCF$_3$, NHCOR, alkyl, arylalkyl, OR, NH$_2$, NHR, NR$_2$, SR;

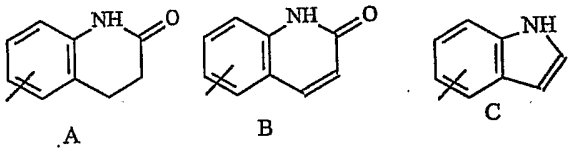
R$_3$ is F, Cl, Br, I, CN, NO$_2$, COR, COOH, CONHR, CF$_3$, SnR$_3$, or R$_3$ together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO$_2$, CN, COR, COOH, or CONHR;

Y is CF$_3$, F, Br, Cl, I, CN, or SnR$_3$;

Q is H, alkyl, halogen, CF$_3$, CN CR$_3$, SnR$_3$, NR$_2$, NHCOCH$_3$, NHCOCF$_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH$_3$, NHCSCF$_3$, NHCSR NHSO$_2$CH$_3$, NHSO$_2$R, OH, OR, COR, OCOR, OSO$_2$R, SO$_2$R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



A B C

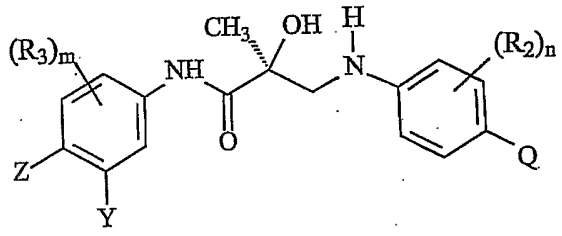
n is an integer of 1-4; and

m is an integer of 1-3.

[00033] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VIII, or any combination thereof.

[00034] In one embodiment, X in formula VIII is NH. In another embodiment, T in formula VIII is OH. In another embodiment, R_1 in formula VIII is CH_3. In another embodiment, G in formula VIII is O. In another embodiment, Z in formula VIII is NO_2. In another embodiment, Z in formula VIII is CN. In another embodiment, Y in formula VIII is CF_3. In another embodiment, Q in formula VIII is $NHCOCH_3$. In another embodiment, Q in formula VIII is F.

[00035] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IX:



IX

wherein Z, Y and Q are as defined above for compound VIII.

[00036] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IX, or any combination thereof.

[00037] In one embodiment, the SARM compound of any of formulas I-IX is an androgen receptor agonist. In another embodiment, the SARM compound of any of formulas I-IX has in-vivo androgenic and anabolic activity for the androgen receptor.

[00038] In one embodiment, the present invention provides a composition comprising the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof.

[00039] In another embodiment, the present invention provides a pharmaceutical composition comprising the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutical product, hydrate or N-oxide or any combination thereof; and a suitable carrier or diluent.

[00040] In another embodiment, the present invention provides a method of binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor.

[00041] In another embodiment, the present invention provides a method of suppressing spermatogenesis in a subject comprising contacting an androgen receptor of the subject with the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production.

[00042] In another embodiment, the present invention provides a method of contraception in a male subject, comprising the step of administering to the subject the

selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

[00043] In another embodiment, the present invention provides a method of hormone therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of any of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[00044] In another embodiment, the present invention provides a method of hormone replacement therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[00045] In another embodiment, the present invention provides a method of treating a subject having a hormone related condition, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[00046] In another embodiment, the present invention provides a method of treating a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

[00047]In another embodiment, the present invention provides a method of preventing prostate cancer in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in the subject.

[00048]In another embodiment, the present invention provides a method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[00049]In another embodiment, the present invention provides a method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in the subject.

[00050] In another embodiment, the present invention provides a method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

[00051] In another embodiment, the present invention provides a method of treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[00052] In another embodiment, the present invention provides a method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

[00053] The novel selective androgen receptor modulator compounds of the present invention, either alone or as a pharmaceutical composition, 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 acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

[00054] The selective androgen receptor modulator compounds of the present invention offer a significant advance over steroidal androgen treatment because the selective androgen receptor modulator compounds of the present invention have been shown in-vivo to have an androgenic and anabolic activity of a nonsteroidal ligand for the

androgen receptor. Thus, the selective androgen receptor modulator compounds have an androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor and will not be accompanied by serious side effects, inconvenient modes of administration, or high costs and still have the advantages of oral bioavailability, lack of cross-reactivity with other steroid receptors, and long biological half-lives.

BRIEF DESCRIPTION OF THE DRAWINGS

[00055]The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawing:

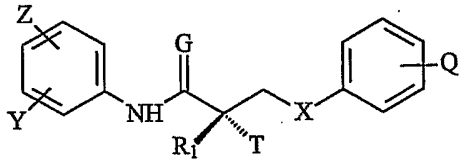
Figure 1: Synthetic scheme of nitrogen-linked selective androgen modulator compounds. a) Acetone/K_2CO_3 reflux b) hexafluoro-isopropanol, reflux.

DETAILED DESCRIPTION OF THE INVENTION

[00056]In one embodiment, this invention provides a class of androgen receptor targeting agents (ARTA). The agents define a new subclass of compounds, which are selective androgen receptor modulators (SARM). Several of the SARM compounds have been found to have an unexpected androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. Other SARM compounds have been found to have an unexpected antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. The SARM compounds, either alone or as a composition, 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 Decline in 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 acute and/or chronic muscular wasting conditions; e) preventing and/or

treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

[00057] In one embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein G is O or S;

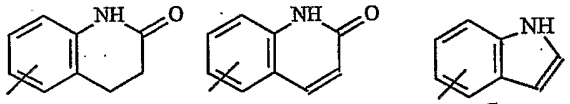
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



A B C

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3.

[00058] In one embodiment, this invention provides an analog of the compound of formula I. In another embodiment, this invention provides a derivative of the compound of formula I. In another embodiment, this invention provides an isomer of the compound of formula I. In another embodiment, this invention provides a metabolite of

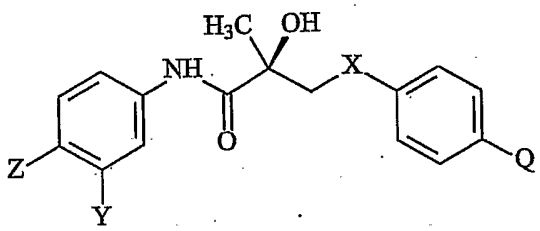
the compound of formula I. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula I. In another embodiment, this invention provides a pharmaceutical product of the compound of formula I. In another embodiment, this invention provides a hydrate of the compound of formula I. In another embodiment, this invention provides an N-oxide of the compound of formula I. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula I.

[00059] In one embodiment, X in formula I is NH. In another embodiment, T in formula I is OH. In another embodiment, R_1 in formula I is CH_3. In another embodiment, G in formula I is O. In another embodiment, Z in formula I is NO_2. In another embodiment, Z in formula I is CN. In another embodiment, Y in formula I is CF_3. In another embodiment, Q in formula I is $NHCOCH_3$. In another embodiment, Q in formula I is F.

[00060] The substituents Z and Y can be in any position of the ring carrying these substituents (hereinafter "A ring"). In one embodiment, the substituent Z is in the para position of the A ring. In another embodiment, the substituent Y is in the meta position of the A ring. In another embodiment, the substituent Z is in the para position of the A ring and substituent Y is in the meta position of the A ring.

[00061] The substituent Q can be in any position of the ring carrying this substituent (hereinafter "B ring"). In one embodiment, the substitutent Q is in the para position of the B ring. In another embodiment, the substitutent Q is $NHCOCH_3$ and is in the para position of the B ring. In another embodiment, the substitutent Q is F and is in the para position of the B ring.

[00062] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



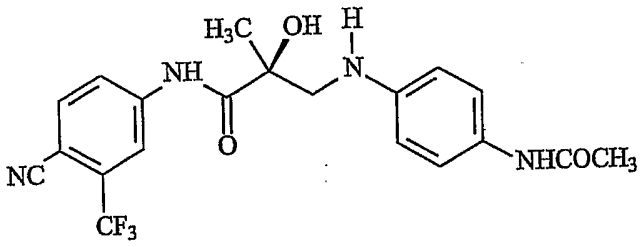
II

wherein Z, Y, X and Q are as defined above for compound I.

[00063]In one embodiment, this invention provides an analog of the compound of formula II. In another embodiment, this invention provides a derivative of the compound of formula II. In another embodiment, this invention provides an isomer of the compound of formula II. In another embodiment, this invention provides a metabolite of the compound of formula II. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula II. In another embodiment, this invention provides a pharmaceutical product of the compound of formula II. In another embodiment, this invention provides a hydrate of the compound of formula II. In another embodiment, this invention provides an N-oxide of the compound of formula II. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II.

[00064]In one embodiment, X in formula II is NH. In another embodiment, Z in formula II is NO_2. In another embodiment, Z in formula II is CN. In another embodiment, Y in formula II is CF_3. In another embodiment, Q in formula II is $NHCOCH_3$. In another embodiment, Q in formula II is F.

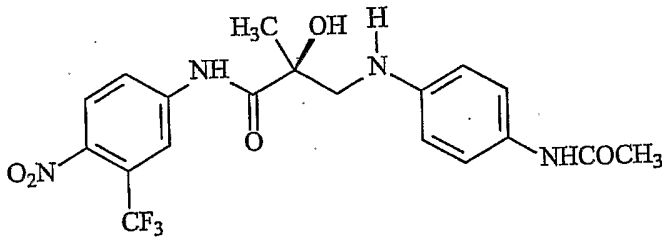
[00065]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



III

[00066]In one embodiment, this invention provides an analog of the compound of formula III. In another embodiment, this invention provides a derivative of the compound of formula III. In another embodiment, this invention provides an isomer of the compound of formula III. In another embodiment, this invention provides a metabolite of the compound of formula III. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula III. In another embodiment, this invention provides a pharmaceutical product of the compound of formula III. In another embodiment, this invention provides a hydrate of the compound of formula III. In another embodiment, this invention provides an N-oxide of the compound of formula III. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula III.

[00067]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:

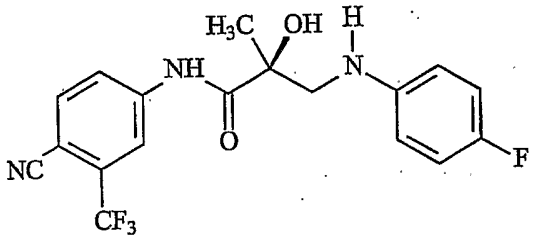


IV

[00068]In one embodiment, this invention provides an analog of the compound of formula IV. In another embodiment, this invention provides a derivative of the compound of formula IV. In another embodiment, this invention provides an isomer of

the compound of formula IV. In another embodiment, this invention provides a metabolite of the compound of formula IV. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula IV. In another embodiment, this invention provides a pharmaceutical product of the compound of formula IV. In another embodiment, this invention provides a hydrate of the compound of formula IV. In another embodiment, this invention provides an N-oxide of the compound of formula IV. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV.

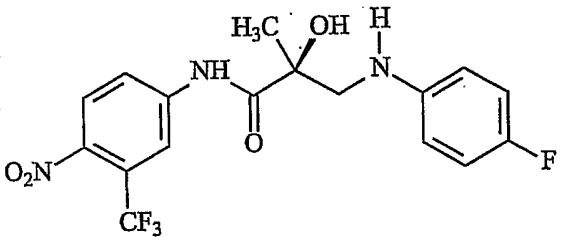
[00069] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula V:



V

[00070] In one embodiment, this invention provides an analog of the compound of formula V. In another embodiment, this invention provides a derivative of the compound of formula V. In another embodiment, this invention provides an isomer of the compound of formula V. In another embodiment, this invention provides a metabolite of the compound of formula V. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula V. In another embodiment, this invention provides a pharmaceutical product of the compound of formula V. In another embodiment, this invention provides a hydrate of the compound of formula V. In another embodiment, this invention provides an N-oxide of the compound of formula V. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula V.

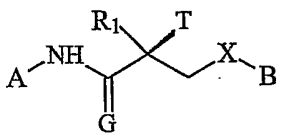
[00071]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VI:



VI

[00072]In one embodiment, this invention provides an analog of the compound of formula VI. In another embodiment, this invention provides a derivative of the compound of formula VI. In another embodiment, this invention provides an isomer of the compound of formula VI. In another embodiment, this invention provides a metabolite of the compound of formula VI. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula VI. In another embodiment, this invention provides a pharmaceutical product of the compound of formula VI. In another embodiment, this invention provides a hydrate of the compound of formula VI. In another embodiment, this invention provides an N-oxide of the compound of formula VI. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VI.

[00073]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VII:



VII

wherein G is O or S;

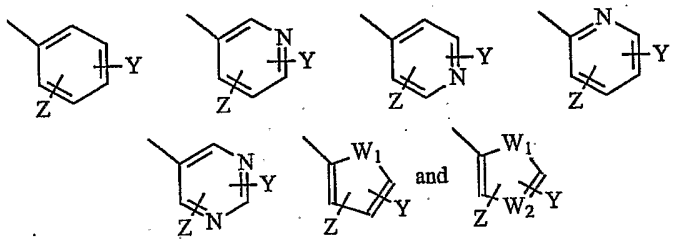
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

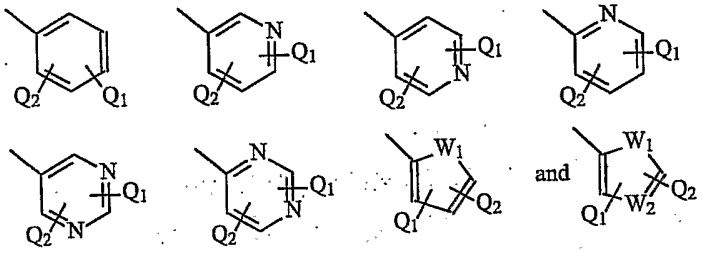
R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:

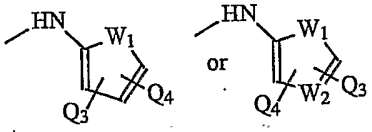


wherein A and B cannot simultaneously be a benzene ring;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 and Q_2 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO,



Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN or NCO;

W_1 is O, NH, NR, NO or S; and

W_2 is N or NO.

[00074]In one embodiment, this invention provides an analog of the compound of formula VII. In another embodiment, this invention provides a derivative of the compound of formula VII. In another embodiment, this invention provides an isomer of the compound of formula VII. In another embodiment, this invention provides a metabolite of the compound of formula VII. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula VII. In another embodiment, this invention provides a pharmaceutical product of the compound of formula VII. In another embodiment, this invention provides a hydrate of the compound of formula VII. In another embodiment, this invention provides an N-oxide of the compound of formula VII. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VII.

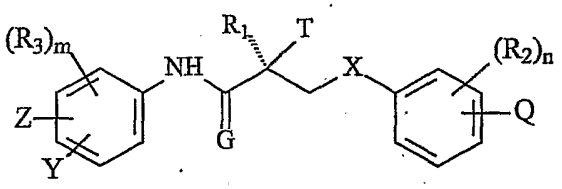
[00075]In one embodiment, X in formula VII is NH. In another embodiment, T in formula VII is OH. In another embodiment, R_1 in formula VII is CH_3. In another embodiment, G in formula VII is O. In another embodiment, Z in formula VII is NO_2. In another embodiment, Z in formula VII is CN. In another embodiment, Y in formula VIII is CF_3. In another embodiment, Q_1 in formula VII is $NHCOCH_3$. In another embodiment, Q_1 in formula VII is F.

[00076]The substituents Z and Y can be in any position of the ring carrying these substituents ("A ring"). In one embodiment, the substituent Z is in the para position of the A ring. In another embodiment, the substituent Y is in the meta position of the A ring. In another embodiment, the substituent Z is in the para position of the A ring and substituent Y is in the meta position of the A ring.

[00077]The substituents Q_1 and Q_2 can be in any position of the ring carrying these substituents ("B ring"). In one embodiment, the substitutent Q_1 is in the para position of the B ring. In another embodiment, the subsituent is Q2 is H. In another embodiment,

the substitutent Q_1 is in the para position of the B ring and the subsituent is Q2 is H. In another embodiment, the substitutent Q_1 is $NHCOCH_3$ and is in the para position of the B ring, and the substituent is Q2 is H. In another embodiment, the substitutent Q_1 is F and is in the para position of the B ring, and the substituent is Q_2 is H.

[00078]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula VIII:



VIII

wherein X is NH, NO or NR;

G is O or S;

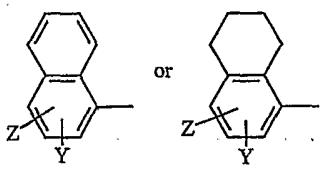
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:

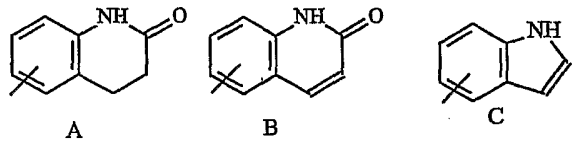


Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

Q is H, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,

$NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OH, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



A B C

n is an integer of 1-4; and

m is an integer of 1-3.

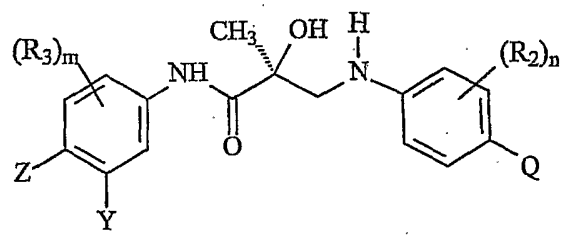
[00079]In one embodiment, this invention provides an analog of the compound of formula VIII. In another embodiment, this invention provides a derivative of the compound of formula VIII. In another embodiment, this invention provides an isomer of the compound of formula VIII. In another embodiment, this invention provides a metabolite of the compound of formula VIII. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula VIII. In another embodiment, this invention provides a pharmaceutical product of the compound of formula VIII. In another embodiment, this invention provides a hydrate of the compound of formula VIII. In another embodiment, this invention provides an N-oxide of the compound of formula VIII. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula VIII.

[00080]In one embodiment, X in formula VIII is NH. In another embodiment, T in formula VIII is OH. In another embodiment, R_1 in formula VIII is CH_3. In another embodiment, G in formula VIII is O. In another embodiment, Z in formula VIII is NO_2. In another embodiment, Z in formula VIII is CN. In another embodiment, Y in formula VIII is CF_3. In another embodiment, Q in formula VIII is $NHCOCH_3$. In another embodiment, Q in formula VIII is F.

[00081]The substituents Z and Y can be in any position of the ring carrying these substituents ("A ring"). In one embodiment, the substituent Z is in the para position of the A ring. In another embodiment, the substituent Y is in the meta position of the A ring. In another embodiment, the substituent Z is in the para position of the A ring and substituent Y is in the meta position of the A ring.

[00082]The substituent Q can be in any position of the ring carrying this substituent ("B ring"). In one embodiment, the substitutent Q is in the para position of the B ring. In another embodiment, the substitutent Q is $NHCOCH_3$ and is in the para position of the B ring. In another embodiment, the substitutent Q is F and is in the para position of the B ring.

[00083]In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IX:



IX

wherein Z, Y and Q are as defined above for compound VIII.

[00084]In one embodiment, this invention provides an analog of the compound of formula IX. In another embodiment, this invention provides a derivative of the compound of formula IX. In another embodiment, this invention provides an isomer of the compound of formula IX. In another embodiment, this invention provides a metabolite of the compound of formula IX. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula IX. In another embodiment, this invention provides a pharmaceutical product of the compound of formula IX. In another embodiment, this invention provides a hydrate of the compound of formula IX. In another embodiment, this invention provides an N-oxide of the compound of formula IX. In another embodiment, this invention provides a combination

of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IX.

[00085]The substituent R is defined herein as an alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3; aryl, phenyl, halogen, alkenyl, or hydroxyl (OH).

[00086]An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkyl groups. In one embodiment, the alkyl group has 1-12 carbons. In another embodiment, the alkyl group has 1-7 carbons. In another embodiment, the alkyl group has 1-6 carbons. In another embodiment, the alkyl group has 1-4 carbons. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[00087]A "haloalkyl" group refers to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I.

[00088]An "aryl" group refers to an aromatic group having at least one carbocyclic aromatic group or heterocyclic aromatic group, which may be unsubstituted or substituted by one or more groups selected from halogen, haloalkyl, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxy or thio or thioalkyl. Nonlimiting examples of aryl rings are phenyl, naphthyl, pyranyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyridinyl, furanyl, thiophenyl, thiazolyl, imidazolyl, isoxazolyl, and the like.

[00089] A "hydroxyl" group refers to an OH group. An "alkenyl" group refers to a group having at least one carbon to carbon double bond. A halo group refers to F, Cl, Br or I.

[00090]An "arylalkyl" group refers to an alkyl bound to an aryl, wherein alkyl and aryl are as defined above. An example of an aralkyl group is a benzyl group.

[00091] As contemplated herein, the present invention relates to the use of a SARM compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or combinations thereof. In one embodiment, the invention relates to the use of an analog of the SARM compound. In another embodiment, the invention relates to the use of a derivative of the SARM compound. In another embodiment, the invention relates to the use of an isomer of the SARM compound. In another embodiment, the invention relates to the use of a metabolite of the SARM compound. In another embodiment, the invention relates to the use of a pharmaceutically acceptable salt of the SARM compound. In another embodiment, the invention relates to the use of a pharmaceutical product of the SARM compound. In another embodiment, the invention relates to the use of a hydrate of the SARM compound. In another embodiment, the invention relates to the use of an N-oxide of the SARM compound.

[00092] As defined herein, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like.

[00093] In one embodiment, this invention encompasses the use of various optical isomers of the SARM compound. It will be appreciated by those skilled in the art that the SARMs of the present invention contain at least one chiral center. Accordingly, the SARMs used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereroisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of androgen-related conditions described herein. In one embodiment, the SARMs are the pure (R)-isomers. In another embodiment, the SARMs are the pure (S)-isomers. In another embodiment, the SARMs are a mixture of the (R) and the (S) isomers. In another embodiment, the SARMs are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by

recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[00094] The invention includes pharmaceutically acceptable salts of amino-substituted compounds with organic and inorganic acids, for example, citric acid and hydrochloric acid. The invention also includes N-oxides of the amino substituents of the compounds described herein. Pharmaceutically acceptable salts can also be prepared from the phenolic compounds by treatment with inorganic bases, for example, sodium hydroxide. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[00095] This invention further includes derivatives of the SARM compounds. The term "derivatives" includes but is not limited to ether derivatives, acid derivatives, amide derivatives, ester derivatives and the like. In addition, this invention further includes hydrates of the SARM compounds. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

[00096] This invention further includes metabolites of the SARM compounds. The term "metabolite" means any substance produced from another substance by metabolism or a metabolic process.

[00097] This invention further includes pharmaceutical products of the SARM compounds. The term "pharmaceutical product" means a composition suitable for pharmaceutical use (pharmaceutical composition), as defined herein.

Biological Activity of Selective Androgen Modulator Compounds

[00098] The compounds provided herein are a new subclass of compounds which are selective androgen receptor modulators (SARM) which are useful for oral testosterone replacement therapy which have an unexpected *in-vivo* activity for an androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. Further, appropriately substituted compounds are effective to treat prostate cancer and are useful

for imaging of prostate cancer. The SARM compounds demonstrate an *in-vivo* androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor.

[00099] As contemplated herein, the appropriately substituted SARM compounds of the present invention 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 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 acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; and/or g) decreasing the incidence of, halting or causing a regression of prostate cancer.

[000100] As used herein, receptors for extracellular signaling molecules are collectively referred to as "cell signaling receptors". Many cell signaling receptors are transmembrane proteins on a cell surface; when they bind an extracellular signaling molecule (i.e., a ligand), they become activated so as to generate a cascade of intracellular signals that alter the behavior of the cell. In contrast, in some cases, the receptors are inside the cell and the signaling ligand has to enter the cell to activate them; these signaling molecules therefore must be sufficiently small and hydrophobic to diffuse across the plasma membrane of the cell.

[000101] Steroid hormones are one example of small hydrophobic molecules that diffuse directly across the plasma membrane of target cells and bind to intracellular cell signaling receptors. These receptors are structurally related and constitute the intracellular receptor superfamily (or steroid-hormone receptor superfamily). Steroid hormone receptors include progesterone receptors, estrogen receptors, androgen

receptors, glueocorticoid receptors, and mineralocorticoid receptors. The present invention is particularly directed to androgen receptors.

[000102] In addition to ligand binding to the receptors, the receptors can be blocked to prevent ligand binding. When a substance binds to a receptor, the three-dimensional structure of the substance fits into a space created by the three- dimensional structure of the receptor in a ball and socket configuration. The better the ball fits into the socket, the more tightly it is held. This phenomenon is called affinity. If the affinity of a substance is greater than the original hormone, it will compete with the hormone and bind the binding site more frequently. Once bound, signals may be sent through the receptor into the cells, causing the cell to respond in some fashion. This is called activation. On activation, the activated receptor then directly regulates the transcription of specific genes. But the substance and the receptor may have certain attributes, other than affinity, in order to activate the cell. Chemical bonds between atoms of the substance and the atoms of the receptors may form. In some cases, this leads to a change in the configuration of the receptor, which is enough to begin the activation process (called signal transduction).

[000103] In one embodiment, the present invention is directed to selective androgen receptor modulator compounds which are agonist compounds. A receptor agonist is a substance which binds receptors and activates them. Thus, in one embodiment, the SARM compounds of the present invention are useful in binding to and activating steroidal hormone receptors. In one embodiment, the agonist compound of the present invention is an agonist which binds the androgen receptor. In another embodiment, the compound has high affinity for the androgen receptor. In another embodiment, the agonist compound also has anabolic activity. In another embodiment, the present invention provides selective androgen modulator compounds which have agonistic and anabolic activity of a nonsteroidal compound for the androgen receptor.

[000104] In another embodiment, other selective androgen receptor modulator compounds are antagonist compounds. A receptor antagonist is a substance which binds receptors and inactivates them. Thus, in one embodiment, the SARM compounds of the

present invention are useful in binding to and inactivating steroidal hormone receptors. In one embodiment, the antagonist compound of the present invention is an antagonist which binds the androgen receptor. In another embodiment, the compound has high affinity for the androgen receptor.

[000105] In yet another embodiment, the SARM compounds of the present invention can be classified as partial AR agonist/antagonists. The SARMs are AR agonists in some tissues, to cause increased transcription of AR-responsive genes (e.g. muscle anabolic effect). In other tissues, these compounds serve as inhibitors at the AR to prevent agonistic effects of the native androgens.

[000106] Assays to determine whether the compounds of the present invention are AR agonists or antagonists are well known to a person skilled in the art. For example, AR agonistic activity can be determined by monitoring the ability of the SARM compounds to maintain and/or stimulate the growth of AR containing tissue such as prostate and seminal vesicles, as measured by weight. AR antagonistic activity can be determined by monitoring the ability of the SARM compounds to inhibit the growth of AR containing tissue.

[000107] The compounds of the present invention bind either reversibly or irreversibly to an androgen receptor. In one embodiment, the androgen receptor is an androgen receptor of a mammal. In another embodiment, the androgen receptor is an androgen receptor of a human. In one embodiment, the SARM compounds bind reversibly to the androgen receptor of a mammal, for example a human. Reversible binding of a compound to a receptor means that a compound can detach from the receptor after binding.

[000108] In another embodiment, the SARM compounds bind irreversibly to the androgen receptor of a mammal, for example a human. Thus, in one embodiment, the compounds of the present invention may contain a functional group (e.g. affinity label) that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in this case, the compounds are alkylating agents which bind irreversibly to the receptor

and, accordingly, cannot be displaced by a steroid, such as the endogenous ligands DHT and testosterone. An "alkylating agent" is defined herein as an agent which alkylates (forms a covalent bond) with a cellular component, such as DNA, RNA or enzyme. It is a highly reactive chemical that introduces alkyl radicals into biologically active molecules and thereby prevents their proper functioning. The alkylating moiety is an electrophilic group that interacts with nucleophilic moieties in cellular components.

[000109] According to one embodiment of the present invention, a method is provided for binding the SARM compounds of the present invention to an androgen receptor by contacting the receptor with a SARM compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, under conditions effective to cause the selective androgen receptor modulator compound to bind the androgen receptor. The binding of the selective androgen receptor modulator compounds to the androgen receptor enables the compounds of the present invention to be useful as a male contraceptive and in a number of hormone therapies. The agonist compounds bind to and activate the androgen receptor. The antagonist compounds bind to and inactivate the androgen receptor. Binding of the agonist or antagonist compounds is either reversible or irreversible.

[000110] According to one embodiment of the present invention, a method is provided for suppressing spermatogenesis in a subject by contacting an androgen receptor of the subject with a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and suppress spermatogenesis.

[000111] According to another embodiment of the present invention, a method is provided for contraception in a male subject, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or

N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

[000112] According to another embodiment of the present invention, a method 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 SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000113] According to another embodiment of the present invention, a method is provided for hormone replacement therapy in a patient (i.e., one suffering from an androgen- dependent condition) which includes contacting an androgen receptor of a patient with a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000114] According to another embodiment of the present invention, a method is provided for treating a subject having a hormone related condition, which includes administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the SARM compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000115] Androgen- dependent conditions which may be treated according to the present invention include those conditions which are associated with aging, such as

hypogonadism, sarcopenia, erythropoiesis, osteoporosis, and any other conditions later determined to be dependent upon low androgen (e.g., testosterone) levels.

[000116] According to another embodiment of the present invention, a method is provided for treating a subject suffering from prostate cancer, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

[000117] According to another embodiment of the present invention, a method is provided for preventing prostate cancer in a subject, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat prevent prostate cancer in the subject.

[000118] According to another embodiment of the present invention, a method is provided for delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[000119] According to another embodiment of the present invention, a method is provided for preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in the subject.

[000120] According to another embodiment of the present invention, a method is provided for treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject a SARM compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

[000121] Furthermore, stimulation of the Androgen Receptor stimulates the production of tears, and thus the SARM compounds of the present invention may be used to treat dry eye conditions. Therefore, according to another embodiment of the present invention, a method is provided for treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[000122] According to another embodiment of the present invention, a method is provided for preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

[000123] As defined herein, "contacting" means that the SARM compound of the present invention is introduced into a sample containing the enzyme in a test tube, flask, tissue culture, chip, array, plate, microplate, capillary, or the like, and incubated at a temperature and time sufficient to permit binding of the SARM to the enzyme. Methods for contacting the samples with the SARM or other specific binding components are known to those skilled in the art and may be selected depending on the type of assay

protocol to be run. Incubation methods are also standard and are known to those skilled in the art.

[000124] In another embodiment, the term "contacting" means that the SARM compound of the present invention is introduced into a subject receiving treatment, and the SARM compound is allowed to come in contact with the androgen receptor *in vivo*.

[000125] As used herein, the term "treating" includes preventative as well as disorder remitative treatment. As used herein, the terms "reducing", "suppressing" and "inhibiting" have their commonly understood meaning of lessening or decreasing. As used herein, the term "progression" means increasing in scope or severity, advancing, growing or becoming worse. As used herein, the term "recurrence" means the return of a disease after a remission.

[000126] As used herein, the term "administering" refers to bringing a subject in contact with a SARM 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.

[000127] The term "libido, as used herein, means sexual desire.

[000128] The term "erectile", as used herein, means capable of being erected. 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.

[000129] "Hypogonadism" is a condition resulting from or characterised by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. "Osteopenia" refers to decreased calcification or density of bone. This is a term which encompasses all skeletal systems in which such a condition is noted.

[000130] "Osteoporosis" refers to a thinning of the bones with reduction in bone mass due to depletion of calcium and bone protein. Osteoporosis predisposes a person to fractures, which are often slow to heal and heal poorly. Unchecked osteoporosis can lead to changes in posture, physical abnormality, and decreased mobility.

[000131] "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.

[000132] "Cognition" refers to the process of knowing, specifically the process of being aware, knowing, thinking, learning and judging. Cognition is related to the fields of psychology, linguistics, computer science, neuroscience, mathematics, ethology and philosophy. The term "mood" refers to a temper or state of the mind. As contemplated herein, alterations means any change for the positive or negative, in cognition and/or mood.

[000133] The term "depression" refers to an illness that involves the body, mood and thoughts, that affects the way a person eats, sleeps and the way one feels about oneself, and thinks about things. The signs and symptoms of depression include loss of interest in activities, loss of appetite or overeating, loss of emotional expression, an empty mood, feelings of hopelessness, pessimism, guilt or helplessness, social withdrawal, fatigue, sleep disturbances, trouble concentrating, remembering, or making decisions, restlessness, irritability, headaches, digestive disorders or chronic pain.

[000134] The term "hair loss", medically known as alopecia, refers to baldness as in the very common type of male-pattern baldness. Baldness typically begins with patch hair loss on the scalp and sometimes progresses to complete baldness and even loss of body hair. Hair loss affects both males and females.

[000135] "Anemia" refers to the condition of having less than the normal number of red blood cells or less than the normal quantity of hemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, decreased. Persons with anemia may feel tired and fatigue easily, appear pale, develop palpitations and become usually short of breath. Anemia is caused by four basic factors: a) hemorrhage (bleeding); b) hemolysis (excessive destruction of red blood cells); c) underproduction of red blood cells; and d) not enough normal hemoglobin. There are many forms of anemia, including aplastic anemia, benzene poisoning, Fanconi anemia, hemolytic disease of the newborn, hereditary spherocytosis, iron deficiency anemia, osteopetrosis, pernicious anemia, sickle cell disease, thalassemia, myelodysplastic syndrome, and a variety of bone marrow diseases. As contemplated herein, the SARM compounds of the present invention are useful in preventing and/or treating any one or more of the above-listed forms of anemia.

[000136] "Obesity" refers to the state of being well above one's normal weight. Traditionally, a person is considered to be obese if they are more than 20 percent over their ideal weight. Obesity has been more precisely defined by the National Institute of Health (NIH) as a Body to Mass Index (BMI) of 30 or above. Obesity is often multifactorial, based on both genetic and behavioral factors. Overweight due to obesity is a significant contributor to health problems. It increases the risk of developing a number of diseases including: Type 2 (adult-onset) diabetes; high blood pressure (hypertension); stroke (cerebrovascular accident or CVA); heart attack (myocardial infarction or MI); heart failure (congestive heart failure); cancer (certain forms such as cancer of the prostate and cancer of the colon and rectum); gallstones and gallbladder disease (cholecystitis); Gout and gouty arthritis; osteoarthritis (degenerative arthritis) of the knees, hips, and the lower back; sleep apnea (failure to breath normally during sleep,

lowering blood oxygen); and Pickwickian syndrome (obesity, red face, underventilation and drowsiness). As contemplated herein, the term "obesity" includes any one of the above-listed obesity-related conditions and diseases. Thus the SARM compounds of the present invention are useful in preventing and/or treating obesity and any one or more of the above-listed obesity-related conditions and diseases.

[000137] "Prostate cancer" is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Over sixty percent of newly diagnosed cases of prostate cancer are found to be pathologically advanced, with no cure and a dismal prognosis. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer.

~~[000138] In one embodiment, the methods of the present invention comprise~~ administering a SARM compound as the sole active ingredient. However, also encompassed within the scope of the present invention are methods for hormone therapy, for treating prostate cancer, for delaying the progression of prostate cancer, and for preventing and/or treating the recurrence of prostate cancer, which comprise administering the SARM compounds in combination with one or more therapeutic agents. These agents include, but are not limited to: 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.

[000139] Thus, in one embodiment, the methods of the present invention comprise administering the selective androgen receptor modulator compound, in combination with

an LHRH analog. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a reversible antiandrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an antiestrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an anticancer drug. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an aromatase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progestin. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an agent acting through other nuclear hormone receptors. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a selective estrogen receptor modulators (SERM). In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progesterone. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an estrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a PDE5 inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with apomorphine. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a bisphosphonate. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with one or more additional SARMS.

[000140] In one embodiment, the present invention provides a composition and a pharmaceutical composition comprising the selective androgen receptor modulator compound of any of formulas I-IX and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof; and a suitable carrier or diluent.

[000141] As used herein, "pharmaceutical composition" means therapeutically effective amounts of the SARM together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or Lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl., acetate, phosphate), 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), solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic 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. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils).

[000142] Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally,

intramuscularly, intravenously, intradermally, subcutaneously, intravaginally, intraperitonealy, intraventricularly, intracranially or intratumorally.

[000143] Further, as used herein "pharmaceutically acceptable carriers" are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media.

[000144] Parenteral vehicles 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. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

[000145] Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). 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.

[000146] Other embodiments of the compositions of the invention incorporate particulate forms, protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral.

[000147] 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 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 abducts less frequently or in lower doses than with the unmodified compound.

[000148] 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 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (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. 115-138 (1984). Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990).

[000149] The pharmaceutical preparation can comprise the SARM agent alone, or can further include a pharmaceutically acceptable carrier and can be in solid or liquid form such as tablets, powders, capsules, pellets, solutions, suspensions, elixirs, emulsions, gels, creams, or suppositories, including rectal and urethral suppositories. Pharmaceutically acceptable carriers include gums, starches, sugars, cellulosic materials, and mixtures thereof. The pharmaceutical preparation containing the SARM agent can be administered to a subject by, for example, subcutaneous implantation of a pellet; in one embodiment, the pellet provides for controlled release of SARM agent over a period of time. The preparation can also be administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation, oral administration of a liquid or solid

preparation, or by topical application. Administration can also be accomplished by use of a rectal suppository or a urethral suppository.

[000150] The pharmaceutical preparations of the invention can be prepared by known dissolving, mixing, granulating, or tablet-forming processes. For oral administration, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like 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. Examples of suitable inert vehicles are conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders such as acacia, cornstarch, gelatin, with disintegrating agents such as cornstarch, potato starch, alginic acid, or with a lubricant such as stearic acid or magnesium stearate.

[000151] Examples of suitable oily vehicles or solvents are vegetable or animal oils such as sunflower oil or fish-liver oil. Preparations can be effected both as dry and as wet granules. For parenteral administration (subcutaneous, intravenous, intraarterial, or intramuscular injection), the SARM agents 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 auxiliaries. Examples are sterile liquids such as water and oils, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. 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.

[000152] The preparation of pharmaceutical compositions which contain an active component is well understood in the art. Typically, such compositions are prepared as aerosols of the polypeptide delivered to the nasopharynx or as injectables, either as liquid solutions or suspensions; however, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be

emulsified. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like or any combination thereof.

[000153] In addition, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents which enhance the effectiveness of the active ingredient.

[000154] 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.

[000155] For topical administration to body surfaces using, for example, creams, gels, drops, and the like, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like can be prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[000156] In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

[000157] For use in medicine, the salts of the SARM may 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.

[000158] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXPERIMENTAL DETAILS SECTION

EXAMPLE 1:

SYNTHESIS OF N-BRIDGED SELECTIVE ANDROGEN MODULATOR COMPOUNDS

A. Chemistry

[000159] N-bridged selective androgen modulator compounds (SARMs) of the present invention were synthesized according to Scheme 1 (Figure 1). Initially, the syntheses were performed in two separate steps – isolating epoxide **(S)-5** before epoxide opening. These steps were combined to a two-step one-pot process where, after the expoxide was formed, the solvent was removed and the resulting residue was immediately carried on tothe opening step. By TLC, the first step goes cleanly and completely to the epoxide. The epoxide was opened with the appropriate substituted aniline in hexafluoro-isopropanol. Aromatic amines are extremely non-nucleophilic; thus the epoxide had to be formed and opened in the presence of hexafluoro-isopropanol, which increases the electrophilicity of the epoxide.

B. Synthesis

[000160] **S-3-(4-Acetylamino-phenylamino)-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethylphenyl)propionamide (S)-16.** (S)-5 (0.075g, 0.26 mmol) and (4-aminophenyl)acetamide (0.04 g, 0.26 mmol) were dissolved in 1.5ml of hexafluoro-2-propanol, and the mixture was allowed to stir at room temperature until the reaction was complete. Completeness of the reaction was monitored by the disappearance of the epoxide starting material, as determined by TLC. The solvent was evaporated, and the residue was diluted with 30ml of water. This aqueous phase was extracted with three 30ml portions of EtOAc. The combined EtOAc extracts were dried over MgSO4, and evaporated to give an oil. By TLC, the oil showed several intense spots. Preparative TLC was used to purify (S)-16 with 10% methanol in chloroform as the mobile phase. The title compound (25mg, 0.06 mmol) was obtained as a tan powder. (27%); mp 143-145°C; ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H, NH), 9.48 (s, 1H, NH), 8.48 (s, 1H, ArH), 9.28 (d, J=9Hz, J-2Hz, 1H, ArH), 8.16 (d, J=9Hz, 1H, ArH), 7.21 (d, J=8Hz, 2H, ArH), 6.57 (d, J=8.0Hz, 2H, ArH), 6.06 (s, 1H, OH), 5.1 (bs, 1H, NH), 3.41 (dd, J-12, 3Hz, 1H, (CH_2(1)), 3.11 (dd, J=12, 3Hz, 1H, (CH_2(2)), 1.93 (s, 3H, Me), 1.41 (s, 3H, Me); Analysis ($C_{19}H_{19}F_3N_4O_5$) Calculated: C 52.74%, H 4.89%, N 11.58%, Found: C 52.4%, H 4.9%, N 11.2%, Calculated Mass 440.13, [M-H]438.8.

[000161] **S-3-(4-Fluoro-phenylamino)-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethylphenyl)propionamide (S)-16.** (S)-5 (0.05g, 0.1 mmol) and (4-fluoroaniline (16 µl, 0.17 mmol) were dissolved in 1ml of hexafluoro-2-propanol, and the mixture was mixed at reflux overnight. The workup was the same as for (S)-15, giving an oil that hardened to a glass on standing. The oil was purified on silica gel column with EtOAc/hexanes (1:1) as the mobile phase to give the title compound as an amber-colored oil (25mg, 0.06 mmol) (36%); ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H, NH), 8.05 (m, 3H, ArH), 6.9 (m, 2H, ArH), 6.7 (m, 2H, ArH), 3.84 (d, J=13Hz, 1H, (CH_2(1)), 3.8 (s, 1H, OH), 3.6 (bs, 1H, NH), 3.24 (d, J=13Hz, 1H, (CH_2(2)), 1.58 (s, 3H, Me); Analysis ($C_{17}H_{15}F_4N_3O_4$.0.25 Acetone) Calculated: C 51.27%, H 4.0%, N 10.10%, Found: C 51.05%, H 3.96%, N 9.90%, Calculated Mass 401, [M-H]400.2

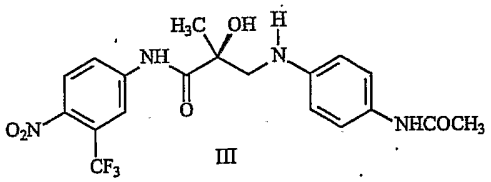
EXAMPLE 2:

ANDROGEN RECEPTOR BINDING AFFINITIES OF N-BRIDGED SELECTIVE ANDROGEN MODULATOR COMPOUNDS

Methods

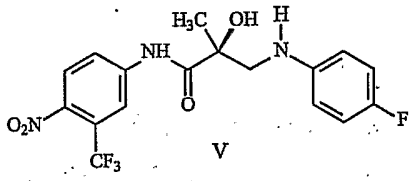
[000162] AR binding affinities were determined using competitive binding assays as described previously (Kirkovsky, L. et al, Chiral nonsteroidal affinity ligands for the androgen receptor. Bicalutamide analogues bearing electrophilic groups in the B aromatic ring. *J. Med. Chem.* 2000, 43, 581-590). Briefly, AR binding studies were performed by incubating increasing concentrations (10^{-3}) nM to 10,000 nM) of each ligand with cytosol, and a saturating concentration of ^{3}H-mibolerone (MIB) (1nm) at 4°C for 18 h. The incubates also contained 1,000 nM triamcinolone acetonide to block interaction of MIB with progesterone receptors. For the determination of non-specific binding, separate experiments were conducted by adding 1,000 nM MIB to the incubate. Separation of bound and free radioactivity at the end of incubation was achieved by the hydroxyapatite method. A 0.8 mL portion of the ethanolic supernatant was added to 5 mL of scintillation cocktail. Radioactivity was counted in a Beckman LS 6800 liquid scintillation counter.

[000163] The Androgen Receptor (AR) binding affinities of the N-bridged compounds (S)-16 and (S-17) were determined.



III

(S)-16



V

(S)-17

[000164] The AR binding affinities are summarized in Table 1. Compound (S)-16 displayed a moderate affinity for the AR, while (S)-17 displayed a high affinity for the AR.

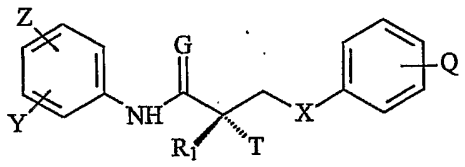
Table 1:

Compound	Ki (nm)
(S)-16	135 ± 12
(S)-17	10 ± 1

[000165] It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow:

WHAT IS CLAIMED IS:

1. A selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein G is O or S;

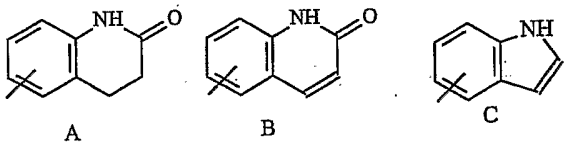
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:

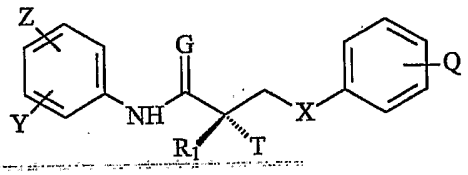


A B C

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3.

2. A selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein G is O or S;

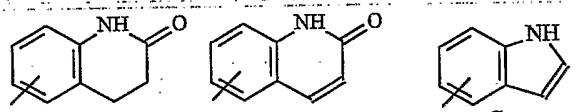
X is NH, NO or NR;

T is OH, OR, -NHCOCH$_3$, or NHCOR

Z is NO$_2$, CN, COOH, COR, NHCOR or CONHR;

Y is CF$_3$, F, I, Br, Cl, CN, CR$_3$ or SnR$_3$;

Q is alkyl, halogen, CF$_3$, CN CR$_3$, SnR$_3$, NR$_2$, NHCOCH$_3$, NHCOCF$_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH$_3$, NHCSCF$_3$, NHCSR NHSO$_2$CH$_3$, NHSO$_2$R, OR, COR, OCOR, OSO$_2$R, SO$_2$R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



A B C

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH$_2$F, CHF$_2$, CF$_3$, CF$_2$CF$_3$, aryl, phenyl, halogen, alkenyl or OH; and

R$_1$ is CH$_3$, CH$_2$F, CHF$_2$, CF$_3$, CH$_2$CH$_3$, or CF$_2$CF$_3$;

or its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

3. The selective androgen receptor modulator compound of claim 1, wherein G is O.

4. The selective androgen receptor modulator compound of claim 1, wherein T is OH.

5. The selective androgen receptor modulator compound of claim 1, wherein R$_1$ is CH$_3$.

6. The selective androgen receptor modulator compound of claim 1, wherein X is NH.

7. The selective androgen receptor modulator compound of claim 1, wherein Z is NO_2.

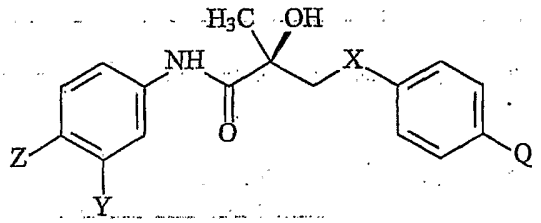
8. The selective androgen receptor modulator compound of claim 1, wherein Z is CN.

9. The selective androgen receptor modulator compound of claim 1, wherein Y is CF_3.

10. The selective androgen receptor modulator compound of claim 1, wherein Q is $NHCOCH_3$.

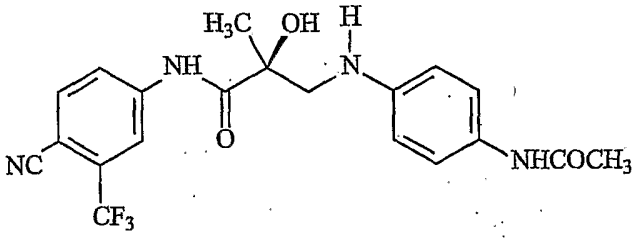
11. The selective androgen receptor modulator compound of claim 1, wherein Q is F.

12. The selective androgen receptor modulator compound of claim 1, represented by the structure of formula II.



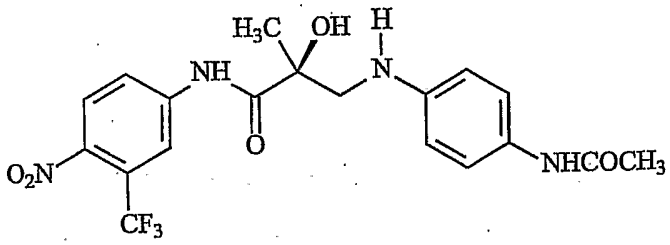
II

13. The selective androgen receptor modulator compound of claim 1, represented by the structure of formula III.



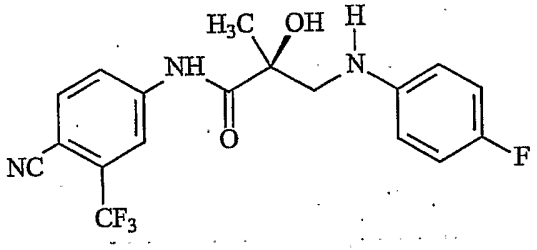
III

14. The selective androgen receptor modulator compound of claim 1, represented by the structure of formula IV.



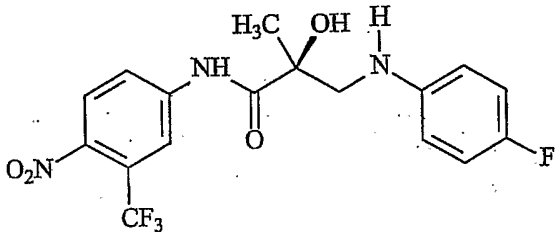
IV

15. The selective androgen receptor modulator compound of claim 1, represented by the structure of formula V.



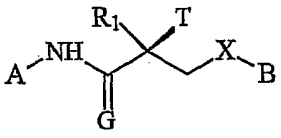
V

16. The selective androgen receptor modulator compound of claim 1, represented by the structure of formula VI.



VI

17. A selective androgen receptor modulator compound represented by the structure of formula VII:



VII

wherein G is O or S;

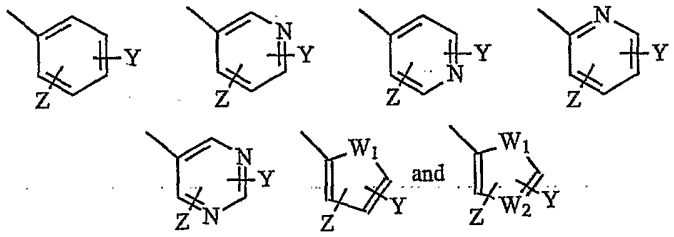
X is NH, NO or NR;

T is OH, OR, -NHCOCH$_3$, or NHCOR

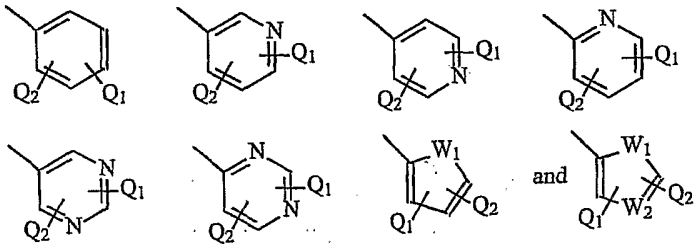
R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:

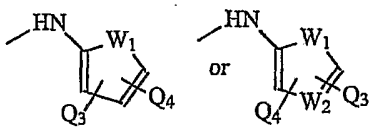


wherein A and B cannot simultaneously be a benzene ring;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 and Q_2 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO,

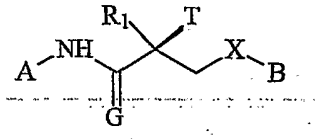


Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN or NCO;

W_1 is O, NH, NR, NO or S; and

W_2 is N or NO.

18. A selective androgen receptor modulator compound represented by the structure of formula VII:



VII

wherein G is O or S;

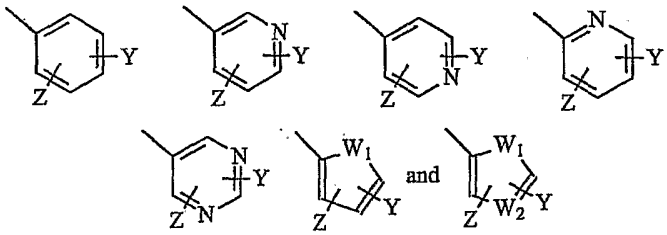
X is NH, NO or NR;

T is OH, OR, -$NHCOCH_3$, or NHCOR

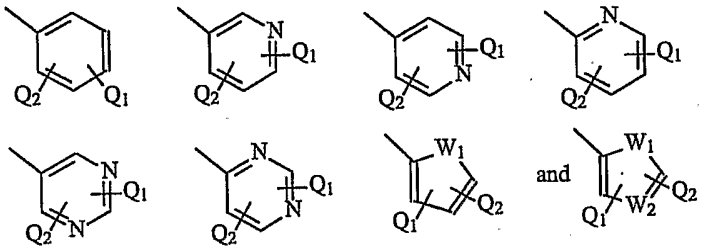
R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:

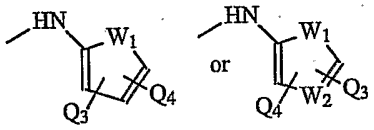


wherein A and B cannot simultaneously be a benzene ring;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 and Q_2 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO,



Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN or NCO;

W_1 is O, NH, NR, NO or S; and

W_2 is N or NO;

or its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

19. The selective androgen receptor modulator compound of claim 17, wherein G is O.

20. The selective androgen receptor modulator compound of claim 17, wherein T is OH.

21. The selective androgen receptor modulator compound of claim 17, wherein R_1 is CH_3.

22. The selective androgen receptor modulator compound of claim 17, wherein X is NH.

23. The selective androgen receptor modulator compound of claim 17, wherein Z is NO_2.

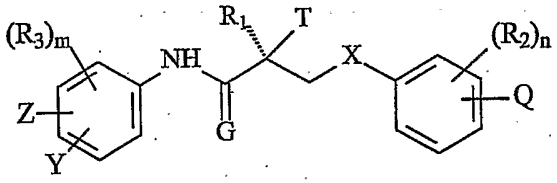
24. The selective androgen receptor modulator compound of claim 17, wherein Z is CN.

25. The selective androgen receptor modulator compound of claim 17, wherein Y is CF_3.

26. The selective androgen receptor modulator compound of claim 17, wherein Q_1 is $NHCOCH_3$.

27. The selective androgen receptor modulator compound of claim 17, wherein Q_1 is F.

28. A selective androgen receptor modulator compound represented by the structure of formula VIII:



VIII

wherein X is NH, NO or NR;

G is O or S;

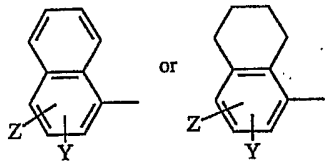
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

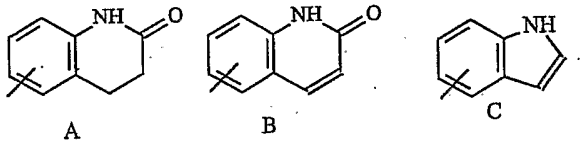
R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

Q is H, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OH, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:

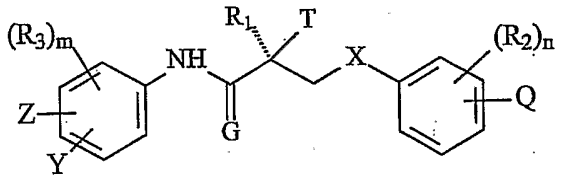


A B C

n is an integer of 1-4; and

m is an integer of 1-3.

29. A selective androgen receptor modulator compound represented by the structure of formula VIII:



VIII

wherein X is NH, NO or NR;

G is O or S;

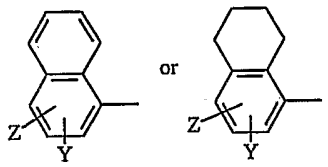
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

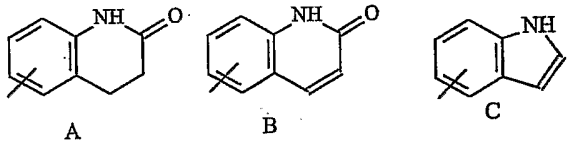
R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

Q is H, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OH, OR, COR, OCOR, OSO_2R, SO_2R, SR, SCN, NCS, OCN, NCO; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



n is an integer of 1-4; and

m is an integer of 1-3;

or its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

30. The selective androgen receptor modulator compound of claim 28, wherein G is O.

31. The selective androgen receptor modulator compound of claim 28, wherein T is OH.

32. The selective androgen receptor modulator compound of claim 28, wherein R_1 is CH_3.

33. The selective androgen receptor modulator compound of claim 28, wherein X is NH.

34. The selective androgen receptor modulator compound of claim 28, wherein Z is NO_2.

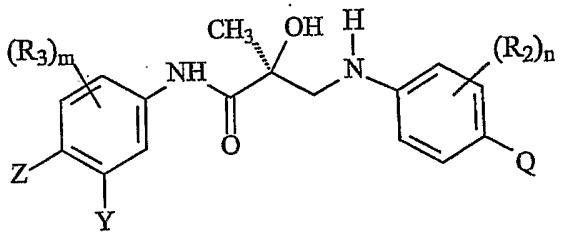
35. The selective androgen receptor modulator compound of claim 28, wherein Z is CN.

36. The selective androgen receptor modulator compound of claim 28, wherein Y is CF_3.

37. The selective androgen receptor modulator compound of claim 28, wherein Q is $NHCOCH_3$.

38. The selective androgen receptor modulator compound of claim 28, wherein Q is F.

39. The selective androgen receptor modulator compound of claim 28, wherein said SARM compound is represented by the structure of formula IX:



IX

40. The selective androgen receptor modulator compound of any of claims 1-39, wherein said compound is an androgen receptor agonist.

41. The selective androgen receptor modulator compound of any of claims 1-39, wherein said compound has in-vivo androgenic and anabolic activity for the androgen receptor.

42. A composition comprising the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof; and a suitable carrier or diluent.

43. A pharmaceutical composition comprising an effective amount of the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical

product, hydrate or N-oxide or any combination thereof; and a pharmaceutically acceptable carrier, diluent or salt.

44. A method of binding a selective androgen receptor modulator compound to an androgen receptor, comprising the step of contacting the androgen receptor with the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor.

45. A method of suppressing spermatogenesis in a subject comprising contacting an androgen receptor of the subject with the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production.

46. A method of contraception in a male subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to suppress sperm production in said subject, thereby effecting contraception in said subject.

47. A method of hormone therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

48. A method of hormone replacement therapy comprising the step of contacting an androgen receptor of a subject with the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

49. A method of treating a subject having a hormone related condition, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

50. A method of treating a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat prostate cancer in said subject.

51. A method of preventing prostate cancer in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in said subject.

52. A method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in said subject.

53. A method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in said subject.

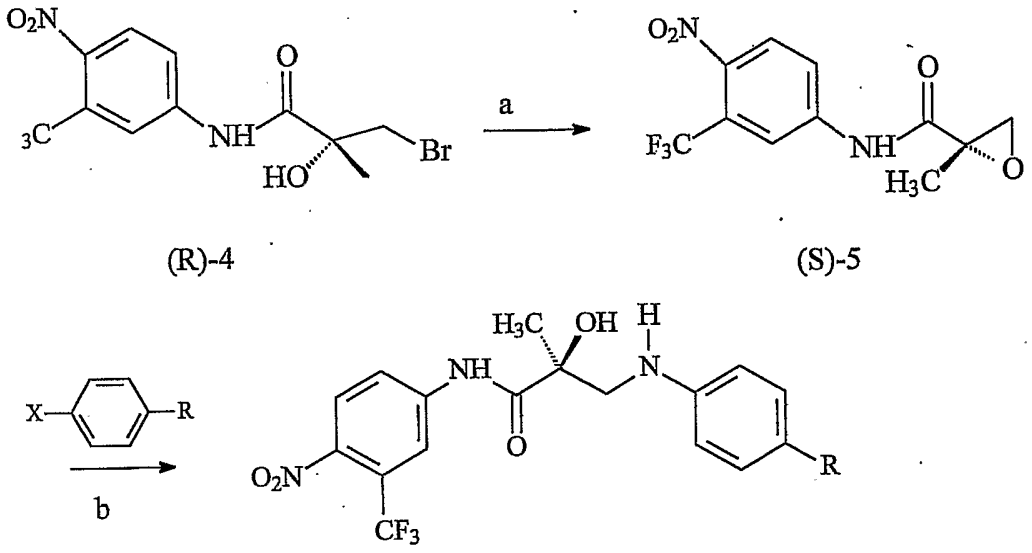
54. A method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to said subject the selective

androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in said subject.

55. A method of treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

56. A method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of any of claims 1-39 and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

Scheme 1:



(S)-16: X = NH, R = $NHCOCH_3$
(S)-17: X = NH, R = F

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/16219

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/158, 153, 157; 546/309; 544/323; 548/326.5; 558/414
514/616, 628, 613, 522, 525, 349, 272, 398

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 6,492,554 B2 (DALTON et al) 10 December 2002, col 14, lines 1-14.	1-16, 28-56
Y	US 6,019,957 A (MILLER et al) 01 February 2000, col. 38 Table 3, and abstract.	1-16 and 28-56
Y	US 4,880,839 A (TUCKER) 14 November 1989, column 1, lines 20-50.	1-16 and 28-56

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
01 OCTOBER 2003

Date of mailing of the international search report
27 OCT 2003

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
SHAILENDRA KUMAR
Telephone No. (703) 308-1235

Janice Ford for

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/16219

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07C 233/05; C07D 211/72, 239/02, 233/44; A61K 31/65, 31/44, 31/505, 31/415

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

564/158, 153, 157; 546/309; 544/323; 548/326.5; 558/414
514/616, 628, 613, 522, 525, 349, 272, 398 .

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/16219

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.