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(71) Applicant(s)
GTX, Inc.

(72) Inventor(s)
Steiner, Mitchell S;Dalton, James T;Miller, Duane D;Veverka, Karen A

(74) Agent / Attorney
Griffith Hack, GPO Box 3125, Brisbane, QLD, 4001

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(71) Applicant (for all designated States except US): GTX, INC. [US/US]; 3 North Dunlap, 3rd Floor, Van Fleet Building, Memphis, TN 38163 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): STEINER, Mitchell, S. [US/US]; 8894 Silverbark Drive, Germantown, TN 38138 (US). VEVERKA, Karen, A. [US/US]; 669 S. Featherwind Cove, Cordova, TN 38018 (US). DALTON, James, T. [US/US]; 2706 Wellesley Drive, Columbus, OH 43221 (US). MILLER, Duane, D. [US/US]; 8706 Maple Creek Cover, Germantown, TN 38139 (US). CHEN, Jiyun [CN/US]; 555 Montgomery Court, Columbus, OH 43210 (US). FISHER, Scott [US/US]; 1969 Merganser Run Drive, Columbus, OH 43215 (US). KIM, Juhyun [KR/US]; 7161 Bunker Hill Blvd #C, Columbus, OH 43215 (US). OKOLICANY, Juraj [SK/US]; 9325 Beaver Valley Lane, Cordova, TN 38018 (US). MARHEFKA, Craig [US/US]; 99 Lewis

Road, Belmont, MA 02478 (US). HWANG, Dong Jin [KR/US]; 1326 Mossbrook Lane #5, Memphis, TN 38134 (US). CHUNG, Kiwon [KR/US]; 530 Warwick Willow Lane, Collierville, TN 38017 (US).

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

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(54) Title: TREATING MUSCLE WASTING WITH SELECTIVE ANDROGEN RECEPTOR MODULATORS

(57) Abstract: This invention provides: a method of treating a subject suffering from a muscle wasting disorder; a method of preventing a muscle wasting disorder in a subject; a method of treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder; a method of treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder; and/or a method of treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, by administering to the subject a selective androgen receptor modulator (SARM) and/or its analog, derivative isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, as described herein.

TREATING MUSCLE WASTING WITH SELECTIVE ANDROGEN RECEPTOR MODULATORS

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FIELD OF INVENTION

[0001] This invention relates to the prevention and treatment of muscle wasting disorders. More particularly, this invention relates to a method of treating, preventing, suppressing, inhibiting, or reducing the incidence of muscle wasting in a 10 subject suffering from a muscle wasting disorder, by administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof.

15

BACKGROUND OF THE INVENTION

[0002] 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.

[0003] The loss of muscle mass that occurs during muscle wasting can be characterized by a muscle protein degradation by catabolism. Protein catabolism occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Muscle protein catabolism, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting.

[0004] Muscle wasting is associated with chronic, neurological, genetic or infectious pathologies, diseases, illnesses or conditions. These include Muscular Dystrophies such as Duchenne Muscular Dystrophy and Myotonic Dystrophy; Muscle Atrophies such as Post-Polio Muscle Atrophy (PPMA); Cachexias such as Cardiac Cachexia, AIDS Cachexia and Cancer Cachexia, malnutrition, Leprosy, Diabetes, Renal Disease, Chronic Obstructive Pulmonary Disease (COPD), Cancer, end stage Renal failure, Sarcopenia, Emphysema, Osteomalacia, HIV Infection, AIDS, and Cardiomyopathy.

[0005] 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.

[0006] An intact androgen receptor (AR) signaling pathway is crucial for appropriate development of skeletal muscles. Furthermore, an intact AR-signalling pathway increases lean muscle mass, muscle strength and muscle protein synthesis.

5 [0007] 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 and poor performance status. In addition, muscle wasting is a strong predictor of morbidity and mortality in patients suffering from cachexia
10 and AIDS. Innovative approaches are urgently needed at both the basic science and clinical levels to prevent and treat muscle wasting, in particular chronic muscle wasting. The present invention is directed to satisfying this need.

15

SUMMARY OF THE INVENTION

[0008] This invention provides: 1) a method of treating a subject suffering from a muscle wasting disorder; 2) a method of preventing a muscle wasting disorder in a subject; 3) a method of treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder; 4) a method of treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder; and/or 5) a method of treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, by administering to the subject a selective androgen receptor modulator (SARM) and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof.

25
30 [0009] Thus, in one embodiment, the present invention provides a method of treating a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM)

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

5 [00010] In another embodiment, the present invention provides a method of preventing a muscle wasting disorder in a subject, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

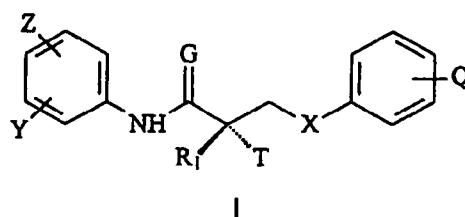
10 [00011] In another embodiment, the present invention provides a method of treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

15 [00012] In another embodiment, the present invention provides a method of treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

20 [00013] In another embodiment, the present invention provides a method of treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

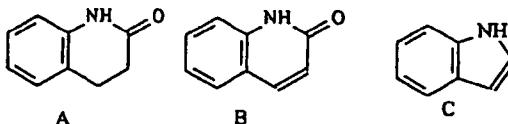
[00014] In one embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula I:

10



15

wherein G is O or S;
X is a bond, O, CH_2 , NH, Se, PR, NO or NR;
T is OH, OR, $-\text{NHCOCH}_3$, or NHCOR
Z is NO_2 , CN, COOH, COR, NHCOR or CONHR ;
Y is CF_3 , F, I, Br, Cl, CN, $\text{C}(\text{R})_3$ or $\text{Sn}(\text{R})_3$;
Q is alkyl, halogen, CF_3 , CN, $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 ,
 NHCOCF_3 , NHCOR , NHCONHR , NHCOOR , OCONHR , CONHR ,
20 NHCSCH_3 , NHCSCF_3 , NHCSR , NHSO_2CH_3 , NHSO_2R , OR, COR,
OCOR, OSO_2R , SO_2R , SR; or Q together with the benzene ring to
which it is attached is a fused ring system represented by structure
A, B or C:

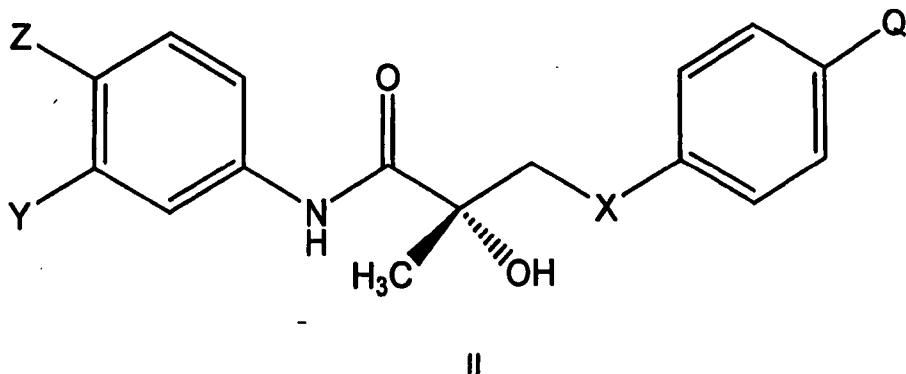


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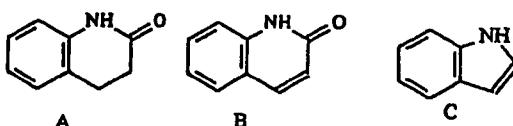
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F , CHF_2 , CF_3 ,
 CF_2CF_3 , aryl, phenyl, halogen, alkenyl or OH; and
 R_1 is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2CH_3 , or CF_2CF_3 .

[00015] In another embodiment, the SARM compound which is effective at 1)

treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula II:



wherein **X** is a bond, O, CH_2 , NH, Se, PR, NO or NR;
Z is NO_2 , CN, COOH, COR, NHCOR or CONHR;
Y is CF_3 , F, I, Br, Cl, CN, $\text{C}(\text{R})_3$ or $\text{Sn}(\text{R})_3$;
Q is alkyl, halogen, CF_3 , CN, $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 ,
 NHCOCF_3 , NHCOR, NHCONHR , NHCOOR , OCONHR , CONHR,
 NHCSCH_3 , NHCSCF_3 , NCSR , NHSO_2CH_3 , NHSO_2R , OR, COR,
OCOR, OSO_2R , SO_2R , SR; or **Q** together with the benzene ring to
which it is attached is a fused ring system represented by structure
A, **B** or **C**;



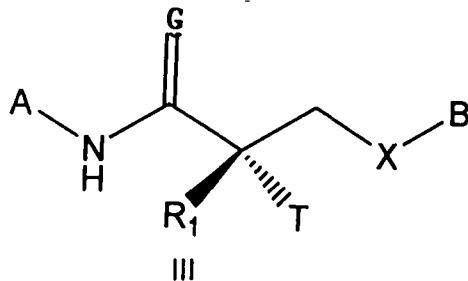
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F , CHF_2 , CF_3 , CF_2CF_3 , aryl, phenyl, halogen, alkenyl or OH.

[00016] In one embodiment, the SARM compound is a compound of formula II wherein X is O. In another embodiment, the SARM compound is a compound of formula II wherein Y is CF₃. In another embodiment, the SARM compound is a

compound of formula II wherein Z is NO_2 . In another embodiment, the SARM compound is a compound of formula II wherein Z is CN. In another embodiment, the SARM compound is a compound of formula II wherein Q is halogen. i.e. F, Cl, Br or I. In another embodiment, the SARM compound is a compound of formula II 5 wherein Q is NHCOCH_3 .

[00017] In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is NO_2 , Y is CF_3 and Q is halogen. In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is NO_2 , Y is CF_3 10 and Q is NHCOCH_3 . In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is CN, Y is CF_3 and Q is halogen. In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is CN, Y is CF_3 15 and Q is NHCOCH_3 .

[00018] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, 20 inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula III:



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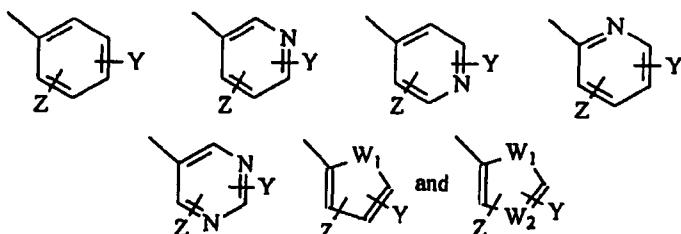
wherein X is a bond, O, CH_2 , NH, Se, PR, NO or NR;
G is O or S;
R₁ is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2CH_3 , or CF_2CF_3 ;

T is OH, OR, -NHCOCH₃, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃,

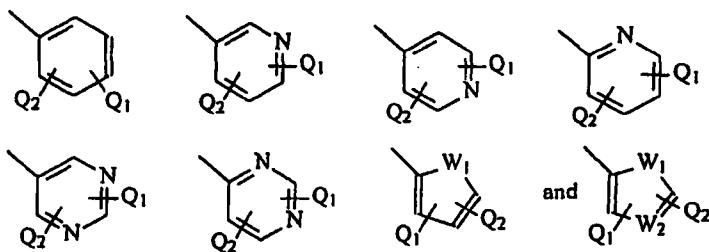
CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



5

B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

Z is NO₂, CN, COOH, COR, NHCOR or CONHR;

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Y is CF₃, F, I, Br, Cl, CN, C(R)₃ or Sn(R)₃;

Q₁ and Q₂ are independently of each other a hydrogen, alkyl,

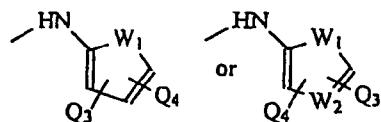
alkyl, halogen, CF₃, CN, C(R)₃, Sn(R)₃, N(R)₂, NHCOCH₃, NHCOCF₃,

NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH₃,

NHCSCF₃, NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR, OCOR,

15

OSO₂R, SO₂R, SR,



Q₃ and Q₄ are independently of each other a hydrogen, alkyl, halogen, CF₃, CN, C(R)₃, Sn(R)₃, N(R)₂, NHCOCH₃, NHCOCF₃, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH₃, NHCSCF₃,

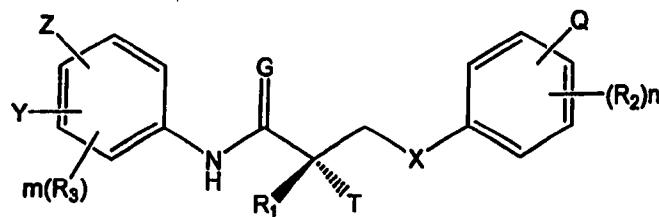
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NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR, OCOR, OSO₂R, SO₂R, SR;

W₁ is O, NH, NR, NO or S; and

W_2 is N or NO.

[00019] In another embodiment, the SARM compound which is effective at 1) 5 treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula IV:



IV

wherein

15 X is a bond, O, CH_2 , NH, Se, PR, NO or NR;

G is O or S;

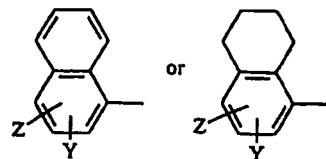
T is OH, OR, $-NHCOCH_3$, or $NHCOR$;

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 ;

20 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 , $N(R)_2$, SR;

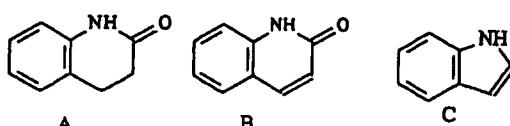
R_3 is F, Cl, Br, I, CN, NO_2 , COR, COOH, CONHR, CF_3 , $Sn(R)_3$, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



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

Y is CF_3 , F, I, Br, Cl, CN, $\text{C}(\text{R})_3$ or $\text{Sn}(\text{R})_3$;

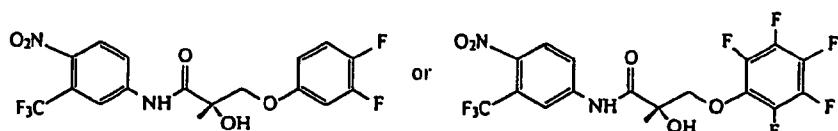
5 Q is H alkyl, halogen, CF_3 , CN, $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 , NHCOCF_3 , NHCOR , NHCONHR , NHCOOR , OCONHR , CONHR , NHCSCH_3 , NHCSCF_3 , NHCSR , NHSO_2CH_3 , NHSO_2R , OH, OR, COR, OCOR, OSO_2R , SO_2R , SR; or Q together with the benzene ring 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.

15 [00020] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, 20 inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is represented by the structure:



[00021] In one embodiment, the administration comprises administering a pharmaceutical composition comprising the SARM, and a pharmaceutically acceptable carrier.

[00022] In one embodiment, the muscle wasting disorder is due to a pathology, illness, disease or condition. In another embodiment, the pathology, illness, disease or condition is chronic. In another embodiment, the pathology, illness, disease or condition is genetic. In another embodiment, the pathology, illness, disease or condition is neurological. In another embodiment, the pathology, illness, disease or condition is infectious.

[00023] In another embodiment, the pathology, illness, disease or condition is a Muscular Dystrophy, a Muscular Atrophy, X-linked spinal-bulbar Muscular Atrophy (SBMA), a Cachexia, malnutrition, Leprosy, Diabetes, Renal Disease, Chronic Obstructive Pulmonary Disease (COPD), Cancer, end stage Renal failure, Sarcopenia, Emphysema, Osteomalacia, HIV Infection, AIDS, or Cardiomyopathy.

[00024] In another embodiment, the muscle wasting disorder is an age-associated muscle wasting disorder, a disuse deconditioning associated muscle wasting disorder, or the muscle wasting disorder occurs due to chronic lower back pain, burns, central nervous system (CNS) injury or damage, peripheral nerve injury or damage, spinal cord injury or damage, chemical injury or damage, or alcoholism. In another embodiment, the muscle wasting disorder is a chronic muscle wasting disorder.

[00025] The present invention provides a safe and effective method for treating, preventing, suppressing, inhibiting or reducing loss of muscle due to muscle wasting and is particularly useful for treating subjects with a muscle wasting disorder, for example a chronic muscle wasting disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

5 **Fig 1:** Effect of androgens on MHC II b mRNA expression from masseter muscle in female rats. A) MHC II b transcript (590 bp) resolved on 1.2% agarose gel with internal control 18S mRNA (488 bp); B) Histogram analysis of control (C, no drug treatment), testosterone propionate (TP), and compound V.

10 **Fig 2:** Effect of testosterone propionate and Compound V on myosin heavy chain (MHC) IIb mRNA expression. Intact male Sprague-Dawley rats were treated with placebo, testosterone propionate (5 mg/kg/day), or Compound V (1 mg/kg/day). Histograms showing effect of Compound V on MHC IIb mRNA expression in Masseter muscle (Top) and Gastrocnemius muscle (Bottom).

15 **Fig 3:** Androgenic and Anabolic activity of Compounds V and VI in rats. Male rats with normal testicular function (no surgical manipulation) were left untreated (Intact), treated with compound V (0.5 mg/day), compound VI (0.5 mg/day) or testosterone propionate (TP, 0.5 mg/day), and the weight of androgen-responsive tissues (prostate – Fig 3A, seminal vesicles – Fig 3B, and levator ani muscle – Fig 3C) were determined.

20 **Fig 4:** Androgenic and Anabolic activity of Compounds V and VI in rats. Male rats received unilateral orchidectomy (Hemi-orchidectomized) and were left untreated (Intact), treated with vehicle alone (PEG 300), Compound V (0.5 mg/day), Compound VI (0.5 mg/day), or testosterone propionate (TP, 0.5 mg/day), and the weight of androgen-responsive tissues (prostate – Fig 4A, seminal vesicles – Fig 4B, and levator ani muscle – Fig 4C) were determined.

25 **Fig 5:** Androgenic and Anabolic activity of Compounds V and VI in rats. Male rats received bilateral orchidectomy (Castrated) and were left untreated

(Intact), treated with vehicle alone (PEG 300), Compound V (0.5 mg/day), Compound VI (0.5 mg/day), or testosterone propionate (TP, 0.5 mg/day), and the weight of androgen-responsive tissues (prostate – Fig 5A, seminal vesicles – Fig 5B, and levator ani muscle – Fig 5C) were determined.

5 **FIG 6:** Dose response curves. Rats were left untreated, or treated with 0.1, 0.3, 10 0.5, 0.75 and 1.0 mg/day Compound V, Compound VI or testosterone propionate (TP), and the weight of androgen-responsive tissues (prostate – Fig 6A, seminal vesicles – Fig 6B and levator ani muscle – Fig 6C) was determined. The results are plotted as percentage of the intact control.

15 **Fig 7:** Dose response curves of Compounds VI-IX in rats. Rats were left untreated, or treated with 0.1, 0.3, 0.5, 0.75 and 1 mg/day of Compound VI (A), Compound VII (B), Compound VIII (C) or Compound IX (D), and the weights of androgen-responsive tissues (prostate and seminal vesicles) and levator ani muscle were determined.

20 **Fig 8:** Dose response curves of Compound X in rats. Castrated rats were left untreated (control), or treated with 0.1, 0.25, 0.5, 0.75 and 1 mg/day of Compound X, and the weights of androgen-responsive tissues (prostate and seminal vesicles) and levator ani muscle were determined. Intact represents male rats with normal testicular function (no surgical manipulation).

25 **Fig 9:** Androgenic and Anabolic activity of Compounds XI and XII in rats. Male rats received bilateral orchidectomy (Castrated) and were left untreated (Castrated Control), or were treated with 1 mg/day Compound XI or compound XII, and the weights of androgen-responsive tissues (prostate and seminal vesicles) and levator ani muscle were determined. Intact represents male rats with normal testicular function (no surgical manipulation).

DETAILED DESCRIPTION OF THE INVENTION

[00026] This invention provides: 1) a method of treating a subject suffering from a muscle wasting disorder; 2) a method of preventing a muscle wasting disorder in a subject; 3) a method of treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder; 4) a method of treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder; and/or 5) a method of treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, by administering to the subject a selective androgen receptor modulator (SARM) and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof.

15 [00027] Thus, in one embodiment, the present invention provides a method of treating a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination 20 thereof.

25 [00028] In another embodiment, the present invention provides a method of preventing a muscle wasting disorder in a subject, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

30 [00029] In another embodiment, the present invention provides a method of treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog,

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

[00030] In another embodiment, the present invention provides a method of treating, 5 preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

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[00031] In another embodiment, the present invention provides a method of treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, comprising the step of administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

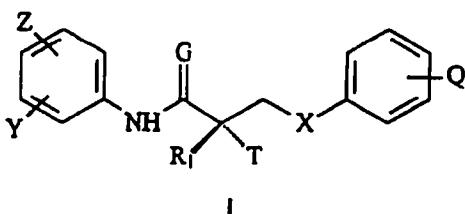
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Selective Androgen Receptor Modulators (SARMS)

[00032] Selective androgen receptor modulators (SARMS) are a class of androgen receptor targeting agents (ARTA), which demonstrate androgenic and anabolic activity of a nonsteroidal ligand for the androgen receptor. These novel agents are useful in males for the treatment of a variety of hormone-related conditions such as sexual dysfunction, decreased sexual libido, erectile dysfunction, hypogonadism, 20 sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, benign prostate hyperplasia and/or prostate cancer. Further, SARMS are useful for oral testosterone replacement therapy, and imaging prostate cancer. In addition, SARMS are useful in females for the treatment of a variety of hormone-related conditions including, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, 25 osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer.

[00033] In one embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula I:

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15

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wherein G is O or S;

X is a bond, O, CH₂, NH, Se, PR, NO or NR;

T is OH, OR, -NHCOCH₃, or NHCOR

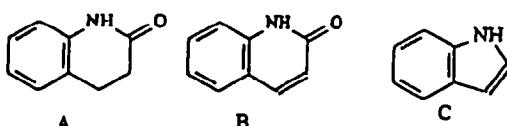
Z is NO₂, CN, COOH, COR, NHCOR or CONHR;

Y is CF₃, F, I, Br, Cl, CN, C(R)₃ or Sn(R)₃;

Q is alkyl, halogen, CF₃, CN C(R)₃, Sn(R)₃, N(R)₂, NHCOCH₃,

NHCOCF₃, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH₃, NHCSCF₃, NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR,

OCOR, OSO₂R, SO₂R, SR; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



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R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃,

CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH; and

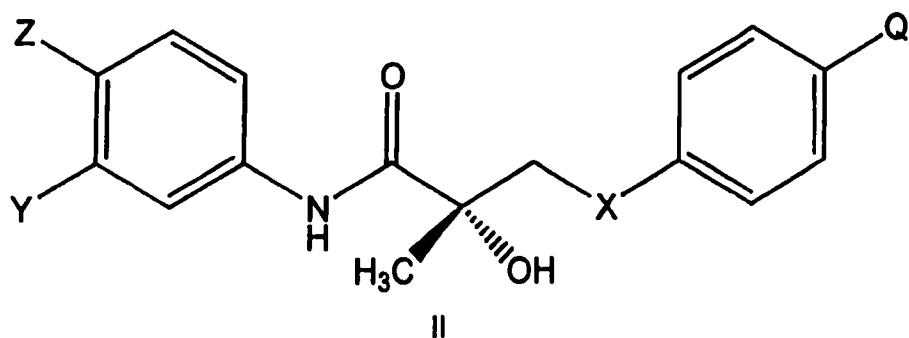
R₁ is CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, or CF₂CF₃.

[00034] In one embodiment, the SARM is an analog of the compound of formula I. In

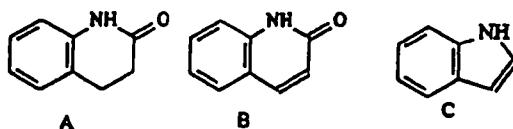
another embodiment, the SARM is a derivative of the compound of formula I. In another embodiment, the SARM is an isomer of the compound of formula I. In another embodiment, the SARM is a metabolite of the compound of formula I. In another embodiment, the SARM is a pharmaceutically acceptable salt of the compound of formula I. In another embodiment, the SARM is a pharmaceutical product of the compound of formula I. In another embodiment, the SARM is a hydrate of the compound of formula I. In another embodiment, the SARM is an N-oxide of the compound of formula I. In another embodiment, the SARM is 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.

[00035] In one embodiment, the SARM compound is a compound of formula I wherein X is O. In one embodiment, the SARM compound is a compound of formula I wherein G is O. In another embodiment, the SARM compound is a compound of formula I wherein Z is NO₂. In another embodiment, the SARM compound is a compound of formula I wherein Z is CN. In another embodiment, the SARM compound is a compound of formula I wherein Y is CF₃. In another embodiment, the SARM compound is a compound of formula I wherein Q is NHCOCH₃. In another embodiment, the SARM compound is a compound of formula I wherein Q is F. In another embodiment, the SARM compound is a compound of formula I wherein T is OH. In another embodiment, the SARM compound is a compound of formula I wherein R₁ is CH₃.

[00036] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula II:



5 wherein X is a bond, O, CH_2 , NH, Se, PR, NO or NR;
 Z is NO_2 , CN, COOH, COR, NHCOR or CONHR;
 Y is CF_3 , F, I, Br, Cl, CN, $\text{C}(\text{R})_3$, or $\text{Sn}(\text{R})_3$;
 Q is alkyl, halogen, CF_3 , CN $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 ,
 NHCOCF_3 , NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,
 10 NHCSCH_3 , NHCSCF_3 , NHCSR , NSO_2CH_3 , NSO_2R , OR, COR,
 OCOR, OSO_2R , SO_2R , SR; or Q together with the benzene ring to
 which it is attached is a fused ring system represented by structure
 A, B or C:



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

[00037] In one embodiment, the SARM is an analog of the compound of formula II. In another embodiment, the SARM is a derivative of the compound of formula II. In 20 another embodiment, the SARM is an isomer of the compound of formula II. In another embodiment, the SARM is a metabolite of the compound of formula II. In another embodiment, the SARM is a pharmaceutically acceptable salt of the compound of formula II. In another embodiment, the SARM is a pharmaceutical product of the compound of formula II. In another embodiment, the SARM is a 25 hydrate of the compound of formula II. In another embodiment, the SARM is an N-oxide of the compound of formula II. In another embodiment, the SARM is a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically

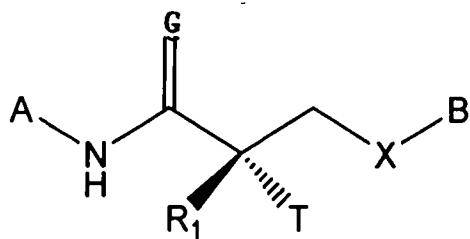
acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II.

[00038] In one embodiment, the SARM compound is a compound of formula II wherein X is O. In another embodiment, the SARM compound is a compound of formula II wherein Z is NO₂. In another embodiment, the SARM compound is a compound of formula II wherein Z is CN. In another embodiment, the SARM compound is a compound of formula II wherein Y is CF₃. In another embodiment, the SARM compound is a compound of formula II wherein Q is NHCOCH₃. In another embodiment, the SARM compound is a compound of formula II wherein Q is F. In another embodiment, the SARM compound is a compound of formula II where Q is halogen, i.e. F, Cl, Br or I.

[00039] In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is NO₂, Y is CF₃ and Q is halogen. In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is NO₂, Y is CF₃ and Q is NHCOCH₃. In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is CN, Y is CF₃ and Q is halogen. In another embodiment, the SARM compound is a compound of formula II wherein X is O, Z is CN, Y is CF₃ and Q is NHCOCH₃.

[00040] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula III:

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III

wherein **X** is a bond, O, CH_2 , NH, Se, PR, NO or NR;

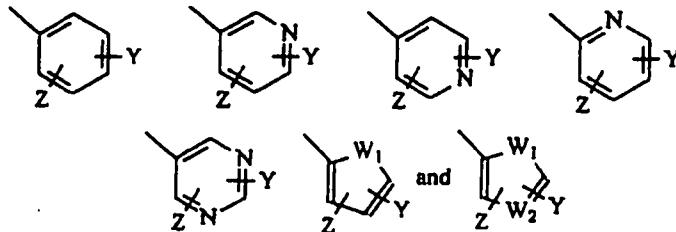
G is O or S;

R₁ is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2CH_3 , or CF_2CF_3 ;

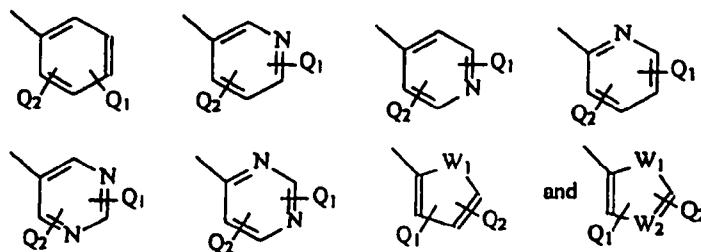
T is OH, OR, - NHCOCH_3 , or NHCOR ;

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

A is a ring selected from:



B is a ring selected from:

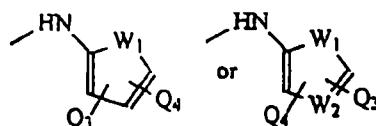


wherein **A** and **B** cannot simultaneously be a benzene ring;

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

Y is CF_3 , F, I, Br, Cl, CN, $\text{C}(\text{R})_3$, or $\text{Sn}(\text{R})_3$;

Q₁ and **Q**₂ are independently of each other a hydrogen, alkyl, halogen, CF_3 , CN, $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 , NHCOCF_3 , NHCOR , NHCONHR , NHCOOR , OCONHR , CONHR , NHCSCH_3 , NHCSF_3 , NHCSR , NHSO_2CH_3 , NHSO_2R , OR, COR, OCOR, OSO₂R, SO₂R, SR,



Q₃ and **Q**₄ are independently of each other a hydrogen, alkyl, halogen, CF_3 , CN, CR_3 , $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 , NHCOCF_3 , NHCOR ,

NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH₃, NHCSCF₃, NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR, OCOR, OSO₂R, SO₂R or SR;

W₁ is O, NH, NR, NO or S; and

5 W₂ is N or NO.

[00041] In one embodiment, the SARM is an analog of the compound of formula III. In another embodiment, the SARM is a derivative of the compound of formula III. In another embodiment, the SARM is an isomer of the compound of formula III. In 10 another embodiment, the SARM is a metabolite of the compound of formula III. In another embodiment, the SARM is a pharmaceutically acceptable salt of the compound of formula III. In another embodiment, the SARM is a pharmaceutical product of the compound of formula III. In another embodiment, the SARM is a hydrate of the compound of formula III. In another embodiment, the SARM is an 15 N-oxide of the compound of formula III. In another embodiment, the SARM is 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.

20 [00042] In one embodiment, the SARM compound is a compound of formula III wherein X is O. In another embodiment, the SARM compound is a compound of formula III wherein G is O. In another embodiment, the SARM compound is a compound of formula I wherein T is OH. In another embodiment, the SARM compound is a compound of formula III wherein R₁ is CH₃. In another embodiment, 25 the SARM compound is a compound of formula III wherein Z is NO₂. In another embodiment, the SARM compound is a compound of formula III wherein Z is CN. In another embodiment, the SARM compound is a compound of formula III wherein Y is CF₃. In another embodiment, the SARM compound is a compound of formula III wherein Q₁ is NHCOCH₃. In another embodiment, the SARM compound is a 30 compound of formula III wherein Q₁ is F.

[00043] 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.

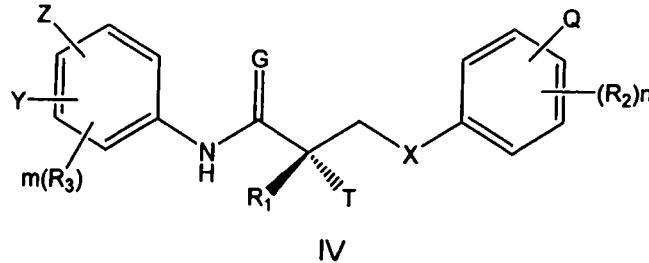
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[00044] The substituents Q₁ and Q₂ can be in any position of the ring carrying these substituents (hereinafter "B ring"). In one embodiment, the substituent Q₁ is in the para position of the B ring. In another embodiment, the substituent is Q₂ is H. In another embodiment, the substituent Q₁ is in the para position of the B ring and the substituent is Q₂ is H. In another embodiment, the substituent Q₁ is NHCOCH₃ and is in the para position of the B ring, and the substituent is Q₂ is H.

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[00045] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) 15 treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula IV:

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wherein X is a bond, O, CH₂, NH, Se, PR, NO or NR;

G is O or S;

T is OH, OR, -NHCOCH₃, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃, CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH;

R₁ is CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, or CF₂CF₃;

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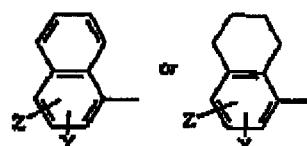
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R_2 is F, Cl, Br, I, CH_3 , CF_3 , OH, CN, NO_2 , $NHCOCH_3$, $NHCOCF_3$, $NHCOR$, alkyl, arylalkyl, OR, NH_2 , NHR , $N(R)_2$, SR;

5

R_3 is F, Cl, Br, I, CN, NO_2 , COR, COOH, CONHR, CF_3 , $Sn(R)_3$, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



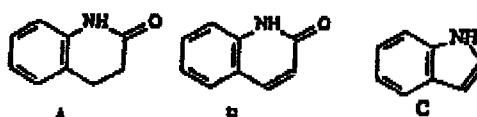
Z is NO_2 , CN, COR, COOH, or CONHR;

10

Y is CF_3 , F, Br, Cl, I, CN or $Sn(R)_3$;

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Q is H, alkyl, halogen, CF_3 , CN, $C(R)_3$, $Sn(R)_3$, $N(R)_2$, $NHCOCH_3$, $NHCOCF_3$, $NHCOR$, $NHCONHR$, $NHCOOR$, $OCONHR$, CONHR, $NHCSCH_3$, $NHSCF_3$, $NHCSR$, $NHSO_2CH_3$, $NHSO_2R$, OH, OR, COR, OCOR, OSO_2R , SO_2R , SR; 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.

20 [00048] In one embodiment, the SARM is an analog of the compound of formula IV. In another embodiment, the SARM is a derivative of the compound of formula IV. In another embodiment, the SARM is an isomer of the compound of formula IV. In another embodiment, the SARM is a metabolite of the compound of formula IV. In another embodiment, the SARM is a pharmaceutically acceptable salt of the compound of formula IV. In another embodiment, the SARM is a pharmaceutical product of the compound of formula IV. In another embodiment, the SARM is a hydrate of the compound of formula IV. In another embodiment, the SARM is an N-oxide of the compound of formula IV. In another embodiment, the SARM is a

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

5 [00047] In one embodiment, the SARM compound is a compound of formula IV wherein X is O. In another embodiment, the SARM compound is a compound of formula IV wherein G is O. In another embodiment, the SARM compound is a compound of formula IV wherein Z is NO₂. In another embodiment, the SARM compound is a compound of formula IV wherein Z is CN. In another embodiment, 10 the SARM compound is a compound of formula IV wherein Y is CF₃. In another embodiment, the SARM compound is a compound of formula IV wherein Q is NHCOCH₃. In another embodiment, the SARM compound is a compound of formula IV wherein Q is F. In another embodiment, the SARM compound is a compound of formula IV wherein T is OH. In another embodiment, the SARM 15 compound is a compound of formula IV wherein R₁ is CH₃. In another embodiment, the SARM compound is a compound of formula IV wherein Q is F and R₂ is CH₃. In another embodiment, the SARM compound is a compound of formula IV wherein Q is F and R₂ is Cl.

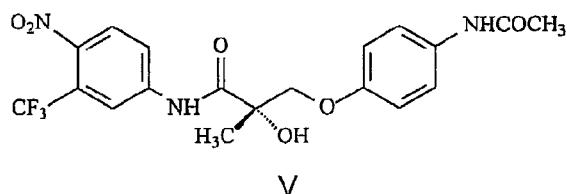
20 [00048] The substituents Z, Y and R₃ can be in any position of the ring carrying these substituents (hereinafter "A ring"). In one embodiment, the substituent Z is in the para position of the A ring. In another embodiment, the substituent Y is in the meta position of the A ring. In another embodiment, the substituent Z is in the para position of the A ring and substituent Y is in the meta position of the A ring.

25 [00049] The substituents Q and R₂ can be in any position of the ring carrying these substituents (hereinafter "B ring"). In one embodiment, the substituent Q is in the para position of the B ring. In another embodiment, the substituent Q is in the para position of the B ring. In another embodiment, the substituent Q is NHCOCH₃ and is in the para position of the B ring.

30 [00050] As contemplated herein, when the integers m and n are greater than one,

the substituents R_2 and R_3 are not limited to one particular substituent, and can be any combination of the substituents listed above.

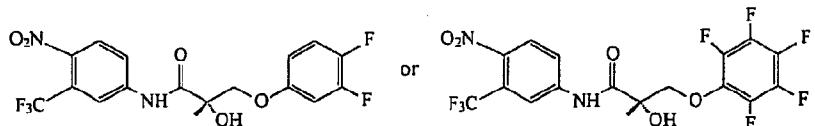
[00051] In another embodiment, the SARM compound which is effective at 1) 5 treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle 10 wasting disorder, is a compound of formula V:



[00052] In one embodiment, the SARM is an analog of the compound of formula V. 15 In another embodiment, the SARM is a derivative of the compound of formula V. In another embodiment, the SARM is an isomer of the compound of formula V. In another embodiment, the SARM is a metabolite of the compound of formula V. In another embodiment, the SARM is a pharmaceutically acceptable salt of the compound of formula V. In another embodiment, the SARM is a pharmaceutical product of the compound of formula V. In another embodiment, the SARM is a hydrate of the compound of formula V. In another embodiment, the SARM is an N-oxide of the compound of formula V. In another embodiment, the SARM is a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of 20 25 formula V.

[00053] In another embodiment, the SARM compound which is effective at 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing 30

muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism due to a muscle wasting disorder, is a compound of formula



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[00054] and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof.

10 [00055] The substituent R in the SARM compounds of the present invention is defined herein as an alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃, CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH.

15 [00056] 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, 20 alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

25 [00057] An "alkenyl" group refers to an unsaturated hydrocarbon, including straight chain, branched chain and cyclic groups having one or more double bond. The alkenyl group may have one double bond, two double bonds, three double bonds etc. Examples of alkenyl groups are ethenyl, propenyl, butenyl, cyclohexenyl etc. The alkenyl 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.

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[00058] 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.

[00059] 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, 10 thiophenyl, thiazolyl, imidazolyl, isoxazolyl, and the like.

[00060] A "hydroxyl" group refers to an OH group. It is understood by a person skilled in the art that when T in the compounds of the present invention is OR, R is not OH. A halo group refers to F, Cl, Br or I.

15

[00061] An "arylalkyl" group refers to an alkyl bound to an aryl, wherein alkyl and aryl are as defined above. An example of an arylalkyl group is a benzyl group.

20

[00062] 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 for the treatment/prevention of muscle wasting disorders. Thus, in one embodiment, the methods of the present invention comprise administering an analog of the SARM. In another embodiment, the methods of the present invention comprise administering a derivative of the SARM. In another embodiment, the methods of the present invention comprise administering an isomer of the SARM. In another embodiment, the methods of the present invention comprise administering a metabolite of the SARM. In another embodiment, the methods of the present invention comprise administering a pharmaceutically acceptable salt of the SARM. In another embodiment, the methods of the present invention comprise administering a pharmaceutical product of the SARM. In another embodiment, the methods of the present invention comprise administering a hydrate of the SARM.

In another embodiment, the methods of the present invention comprise administering an N-oxide of the SARM. In another embodiment, the methods of the present invention comprise administering any of a combination of an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the SARM.

[00063] 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.

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[00064] 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, 15 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 stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of androgen-related conditions described herein. In one embodiment, the SARMs are 20 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 25 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).

[00065] The invention includes "pharmaceutically acceptable salts" of amino-substituted compounds with organic and inorganic acids, for example, citric acid 30 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.

5 [00066] 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.

10 [00067] 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.

15 [00068] 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

20 [00069] As contemplated herein, the SARM compounds of the present invention are useful in treating, preventing, suppressing, inhibiting or reducing the incidence of muscle wasting disorders, as defined herein. An intact androgen receptor (AR) signaling pathway is crucial for appropriate development of skeletal muscles. Furthermore, an intact AR-signalling pathway increases lean muscle mass, muscle strength and muscle protein synthesis.

25 [00070] A muscle is a tissue of the body that primarily functions as a source of power. There are three types of muscles in the body: a) skeletal muscle -the muscle responsible for moving extremities and external areas of the bodies; b) 30 cardiac muscle – the heart muscle; and c) smooth muscle – the muscle that is in the walls of arteries and bowel.

[00071] A wasting condition or disorder is defined herein as a condition or disorder that is characterized, at least in part, by an abnormal, progressive loss of body, organ or tissue mass. A wasting condition can occur as a result of a pathology such as, for example, cancer, or it can be due to a physiologic or metabolic state, such as disuse deconditioning that can occur, for example, due to prolonged bed rest or when a limb is immobilized, such as in a cast. A wasting condition can also be age associated. The loss of body mass that occurs during a wasting condition can be characterized by a loss of total body weight, or a loss of organ weight such as a loss of bone or muscle mass due to a decrease in tissue protein.

10 [00072] The terms "muscle wasting" or "muscular wasting", used herein interchangeably, refer to the progressive loss of muscle mass and/or to the progressive weakening and degeneration of muscles, including the skeletal or voluntary muscles which control movement, cardiac muscles which control the heart, and smooth muscles. In one embodiment, the muscle wasting condition or disorder is a chronic muscle wasting condition or disorder. "Chronic muscle wasting" is defined herein as the chronic (i.e. persisting over a long period of time) progressive loss of muscle mass and/or to the chronic progressive weakening and degeneration of muscle.

15 [00073] The loss of muscle mass that occurs during muscle wasting can be characterized by a muscle protein breakdown or degradation, by muscle protein catabolism. Protein catabolism occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both.

20 [00074] Protein catabolism or depletion, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting. The term "catabolism" has its commonly known meaning in the art, specifically an energy burning form of metabolism.

25 [00075] Muscle wasting can occur as a result of a pathology, disease, condition or disorder. In one embodiment, the pathology, illness, disease or condition is chronic. In another embodiment, the pathology, illness, disease or condition is genetic. In

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

5 [00075] These include but are not limited to Muscular Dystrophies; Muscle Atrophies; Cachexias ; malnutrition, Leprosy, Diabetes, Renal Disease, Chronic Obstructive 10 Pulmonary Disease (COPD), Cancer, end stage Renal failure, Sarcopenia, Emphysema, Osteomalacia, HIV Infection, AIDS, or Cardiomyopathy.

15 [00076] In another embodiment, the muscle wasting disorder is due to an infectious disease such as enterovirus, Epstein-Barr virus, herpes zoster, HIV, trypanosomiasis, influenza, coxsackie, infectious mononucleosis, Rickettsia, Trichinella, or Schistosomiasis.

20 [00077] The muscular dystrophies are genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles that control movement. The muscles of the heart and some other involuntary muscles are also affected in some forms of muscular dystrophy. The major forms of Muscular Dystrophy are: Duchenne Muscular Dystrophy, Myotonic Dystrophy, Duchenne 25 Muscular Dystrophy, Becker Muscular Dystrophy, Limb-girdle Muscular Dystrophy, Facioscapulhumeral Muscular Dystrophy, Congenital Muscular Dystrophy, Oculopharyngeal Muscular Dystrophy, Distal Muscular Dystrophy and Emery-Dreifuss Muscular Dystrophy.

30 [00078] Muscular Dystrophy can affect people of all ages. Although some forms first become apparent in infancy or childhood, others may not appear until middle age or later. Duchenne Muscular Dystrophy is the most common kind of Muscular Dystrophy affecting children. Myotonic Dystrophy is the most common of these diseases in adults.

[00080] Muscle Atrophy is characterized by wasting away or diminution of muscle and a decrease in muscle mass. For example, Post-Polio Muscular Atrophy is a muscle wasting that occurs as part of the Post-Polio Syndrome (PPS). The Atrophy 5 includes weakness, muscle fatigue, and pain.

[00081] Another type of Muscular Atrophy is X-linked spinal-bulbar Muscular Atrophy (SBMA – also known as Kennedy's Disease). This disease arises from a defect in the androgen receptor gene on the X chromosome, affects only males, and its 10 onset is in adulthood. Because the primary disease cause is an androgen receptor mutation, androgen replacement is not a current therapeutic strategy. There are some investigational studies where exogenous testosterone propionate is being given to boost the levels of androgen with hopes of overcoming androgen insensitivity and perhaps provide an anabolic effect. Still, use of 15 supraphysiological levels of testosterone for supplementation will have limitations and other potentially serious complications.

[00082] Cachexia is weakness and a loss of weight caused by a disease or as a side effect of illness. Cardiac Cachexia, i.e. a muscle protein wasting of both the cardiac and skeletal muscle, is a characteristic of congestive heart failure. Cancer Cachexia is a syndrome that occurs in patients with solid tumors and hematological malignancies and is manifested by weight loss with massive depletion of both adipose tissue and lean muscle mass. Acquired Immunodeficiency Syndrome (AIDS). Cachexia is a Human Immunodeficiency Virus (HIV) associated myopathy 20 and/or muscle weakness/wasting that is a relatively common clinical manifestation of AIDS. Individuals with HIV-associated myopathy or muscle weakness or wasting typically experience significant weight loss, generalized or proximal muscle 25 weakness, tenderness, and muscle atrophy.

30 [00083] Sarcopenia is a debilitating disease that afflicts the elderly and chronically ill patients and is characterized by loss of muscle mass and function [Nair K.S. Mayo Clin Proc 2000 Jan; 75 Suppl:S14-8]. It is well established that anabolic steroids

can prevent and/or reverse losses in lean body mass (decrease in skeletal muscle mass) associated with age, disease and trauma injury [Sheffield-Moore, Ann. Med. 32:181-186, 2000; Bhasin, S. Mayo Clin Proc 2000 Jan; 75 Suppl:S70-5]. Further, increased lean body mass is associated with decreased morbidity and mortality for 5 certain muscle-wasting disorders.

[00084] In addition, other circumstances and conditions are linked to, and can cause muscle wasting disorders. For example, studies have shown that in severe cases of chronic lower back pain, there is paraspinal muscle wasting.

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[00085] Muscle wasting is also associated with advanced age. It is believed that general weakness in old age is due to muscle wasting. As the body ages, an increasing proportion of skeletal muscle is replaced by fibrous tissue. The result is a significant reduction in muscle power, performance and endurance.

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[00086] Long term hospitalization due to illness or injury, or disuse deconditioning that occurs, for example, when a limb is immobilized, can also lead to muscle wasting. Studies have shown that in patients suffering injuries, chronic illnesses, burns, trauma or cancer, who are hospitalized for long periods of time, there is a 20 long-lasting unilateral muscle wasting, with a consequent decrease in body mass.

[00087] Injuries or damage to the Central Nervous System (CNS) are also associated with muscle wasting disorders. Injuries or damage to the CNS can be, for example, caused by diseases, trauma or chemicals. Examples are central 25 nerve injury or damage, peripheral nerve injury or damage and spinal cord injury or damage.

[00088] Finally, alcoholism has been shown to be associated with muscle wasting disorders.

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[00089] As contemplated herein, this invention provides a class of compounds which are Selective Androgen Receptor Modulator (SARM) compounds. These

compounds, which are useful in preventing and treating muscle wasting disorders are classified as androgen receptor agonists (AR agonists), partial agonists or androgen receptor antagonists (AR antagonists).

5 [00090] A receptor agonist is a substance which binds receptors and activates them. A receptor partial agonist is a substance which binds receptor and partially activate them. A receptor antagonist is a substance which binds receptors and inactivates them. As demonstrated herein, the SARM compounds of the present invention have a tissue-selective effect, wherein one agent may be an agonist, 10 partial agonist and/or antagonist, depending on the tissue. For example, the SARM compound may stimulate muscle tissue and at the same time inhibit prostate tissue. In one embodiment, the SARMs which are useful in treating and preventing muscle wasting disorders are AR agonists, and are, therefore, useful in binding to and activating the AR. In another embodiment, the SARMs are AR antagonists, and 15 are, therefore, useful in binding to and inactivating the AR. 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, 20 as measured by weight. AR antagonistic activity can be determined by monitoring the ability of the SARM compounds inhibit the growth of AR containing tissue.

[00091] 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 25 some tissues, to cause increased transcription of AR-responsive genes (e.g. muscle anabolic effect). In other tissues, these compounds serve as competitive inhibitors of testosterone/DHT on the AR to prevent agonistic effects of the native androgens.

30 [00092] The SARM compounds of the present invention bind either reversibly or irreversibly to the androgen receptor. In one embodiment, the SARM compounds bind reversibly to the androgen receptor. In another embodiment, the SARM

compounds bind irreversibly to the androgen receptor. The compounds of the present invention may contain a functional group (affinity label) that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in this case, the compounds bind irreversibly to the receptor and, accordingly, cannot be
5 displaced by a steroid, such as the endogenous ligands DHT and testosterone.

[00093] The present invention provides a safe and effective method for treating, preventing, suppressing, inhibiting or reducing loss of muscle and/or muscle protein catabolism due to muscle wasting and is particularly useful for treating a subject suffering from a muscle wasting disorder. In one embodiment, the subject is a 5 mammalian subject. In another embodiment, the subject is a human subject. In another embodiment, the subject is a male subject. In another embodiment, the subject is a female subject.

Pharmaceutical Compositions

[00094] This invention provides the use of a composition and a pharmaceutical composition for treating a subject suffering from a muscle wasting disorder; for preventing a muscle wasting disorder; for treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder; for treating, preventing, inhibiting, reducing or suppressing muscle wasting 15 in a subject suffering from a muscle wasting disorder; and for treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder by administering a selective androgen receptor modulator (SARM) and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any 20 combination thereof; and a pharmaceutically acceptable carrier.

[00095] As used herein, "pharmaceutical composition" means a "therapeutically effective amount" of the active ingredient, i.e. the SARM compound, together with a pharmaceutically acceptable carrier or diluent. A "therapeutically effective amount" 25 as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen.

[00096] The pharmaceutical compositions containing the SARM agent can be administered to a subject by any method known to a person skilled in the art, such 30 as parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intracranially, intravaginally or intratumorally.

[00097] In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e. as a solid or a liquid preparation. Suitable solid oral formulations include tablets, 5 capsules, pills, granules, pellets and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the SARM compounds are formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the SARM active compound and the inert carrier 10 or diluent, a hard gelating capsule.

[00098] Further, in another embodiment, the pharmaceutical compositions are administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation. Suitable liquid formulations include solutions, suspensions, 15 dispersions, emulsions, oils and the like. In one embodiment, the pharmaceutical compositions are administered intravenously, and are thus formulated in a form suitable for intravenous administration. In another embodiment, the pharmaceutical compositions are administered intraarterially, and are thus formulated in a form suitable for intraarterial administration. In another embodiment, the pharmaceutical 20 compositions are administered intramuscularly, and are thus formulated in a form suitable for intramuscular administration.

[00099] Further, in another embodiment, the pharmaceutical compositions are administered topically to body surfaces, and are thus formulated in a form suitable 25 for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

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[00100] Further, in another embodiment, the pharmaceutical compositions are administered as a suppository, for example a rectal suppository or a urethral

suppository. Further, in another embodiment, the pharmaceutical compositions are administered by subcutaneous implantation of a pellet. In a further embodiment, the pellet provides for controlled release of SARM agent over a period of time.

5 [000101] 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.*).

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[000102] As used herein "pharmaceutically acceptable carriers or diluents" are well known to those skilled in the art. The carrier or diluent may be a solid carrier or diluent for solid formuations, a liquid carrier or diluent for liquid formulations, or mixtures thereof.

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[000103] Solid carriers/diluents include, but are not limited to, a gum, a starch (e.g. corn starch, pregeletanized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g. microcrystalline cellulose, carboxymethylcellulose), a cyclodextrin, an acrylate (e.g. polymethylacrylate), 20 calcium carbonate, magnesium oxide, talc, or mixtures thereof.

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[000104] For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil.

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[000105] Parenteral vehicles (for subcutaneous, intravenous, intraarterial, or intramuscular injection) include sodium chloride solution, Ringer's dextrose,

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

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[000106] In addition, the compositions may further comprise binders (e.g. acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g. cornstarch, potato starch, alginic acid, silicon dioxide, croscarmelose sodium, crospovidone, guar gum, sodium starch glycolate), buffers (e.g., Tris-HCl., acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g. sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g. hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g. carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweetners (e.g. aspartame, citric acid), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g. stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g. colloidal silicon dioxide), plasticizers (e.g. diethyl phthalate, triethyl citrate), emulsifiers (e.g. carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g. ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

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[000107] In one embodiment, the pharmaceutical compositions provided herein are controlled release compositions, i.e. compositions in which the SARM compound is

released over a period of time after administration. Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another embodiment, the composition is an immediate release composition, i.e. a composition in which all of the SARM compound is released immediately after 5 administration.

[000108] 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 10 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 15 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).

20 [000109] The compositions may also include incorporation of the active 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 25 compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance.

[000110] Also comprehended by the invention are particulate compositions coated 30 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.

[000111] Also comprehended by the invention are compounds modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline. The 5 modified compounds are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified compounds (Abuchowski et al., 1981; Newmark et al., 1982; and Katre et al., 1987). Such modifications may also increase the compound's solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the 10 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.

15 [000112] The preparation of pharmaceutical compositions which contain an active component is well understood in the art, for example by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the SARM agents or their physiologically 20 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. For parenteral administration, the SARM agents or their physiologically 25 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.

[000113] An active component can be formulated into the composition as neutralized 30 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, 5 trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[000114] For use in medicine, the salts of the SARM will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts.

10 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.

15 [000115] 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.

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[000116] 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*.

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[000117] As used herein, the term "treating" includes preventative as well as disorder remittive 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.

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[000118] 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 10 present invention encompasses administering the compounds of the present invention to a subject.

[000119] In one embodiment, the methods of the present invention comprise administering a SARM compound as the sole active ingredient. However, also 15 encompassed within the scope of the present invention are methods for 1) treating a muscle wasting disorder; 2) preventing a muscle wasting disorder; 3) treating, preventing, suppressing, inhibiting or reducing muscle loss due to a muscle wasting disorder; 4) treating, preventing, inhibiting, reducing or suppressing muscle wasting due to a muscle wasting disorder; and/or 5) treating, preventing, inhibiting, reducing 20 or suppressing muscle protein catabolism due to a muscle wasting disorder, 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, selective estrogen receptor modulators (SERMS), anticancer drugs, 5-alpha reductase inhibitors, aromatase inhibitors, 25 progestins, other selective androgen receptor modulators (SARMS), testosterone, anabolic steroids, growth hormones or agents acting through other nuclear hormone receptors.

[000120] Thus, in one embodiment, the present invention provides compositions and 30 pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an LHRH analog. In another embodiment, the present invention provides compositions and pharmaceutical compositions

comprising a selective androgen receptor modulator compound, in combination with a reversible antiandrogen. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an antiestrogen. In another 5 embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with a SERM. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an anticancer drug. In another 10 embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an aromatase inhibitor. In another embodiment, the present invention provides 15 compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with a progestin. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with another SARM. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with testosterone. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an anabolic steroid. In another embodiment, the 20 present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with a growth hormone. In another embodiment, the present invention provides compositions and pharmaceutical compositions comprising a selective androgen receptor modulator compound, in combination with an agent acting through other 25 nuclear hormone receptors.

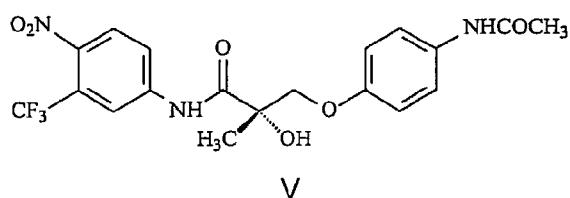
[000121] Various embodiments of dosage ranges are contemplated by this invention.

The dosage may be in the range of 0.1-80 mg/day. In another embodiment, the dosage is in the range of 0.1-50 mg/day. In another embodiment, the dosage is in the range of 0.1-20 mg/day. In another embodiment, the dosage is in the range of 0.1-10 mg/day. In another embodiment, the dosage is in the range of 0.1-5 mg/day. In another embodiment, the dosage is in the range of 0.5-5 mg/day. In another embodiment, the dosage is in the range of 0.5-50 mg/day. In another embodiment, the dosage is be in the range of 5-80 mg/day. In another embodiment, the dosage is in the range of 35-65 mg/day. In another embodiment, the dosage is in the range of 35-65 mg/day. In another embodiment, the dosage is in the range of 20-60 mg/day. In another embodiment, the dosage is in the range of 40-60 mg/day. In another embodiment, the dosage is in a range of 45-60 mg/day. In another embodiment, the dosage is in the range of 40-60 mg/day. In another embodiment, the dosage is in a range of 60-120 mg/day. In another embodiment, the dosage is in the range of 120-240 mg/day. In another embodiment, the dosage is in the range of 40-60 mg/day. In another embodiment, the dosage is in a range of 240-400 mg/day. In another embodiment, the dosage is in a range of 45-60 mg/day. In another embodiment, the dosage is in the range of 15-25 mg/day. In another embodiment, the dosage is in the range of 5-10 mg/day. In another embodiment, the dosage is in the range of 55-65 mg/day. In one embodiment, the dosage is 20 mg/day. In another embodiment, the dosage is 40 mg/day. In another embodiment, the dosage is 60 mg/day.

[000122] The following examples are presented in order to more fully illustrate certain embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXPERIMENTAL DETAILS SECTIONEXAMPLE 15 Effect of Selective Androgen Receptor Modulators (SARMS) and
testosterone on skeletal muscles in intact female rats

10 [000123] Compound V (N-[4-nitro-3-trifluoromethyl)phenyl]- (2S)-3-[4-(acetylamino) phenoxy]-2-hydroxy-2-methylpropanamide), is a selective androgen receptor modulator represented by the formula:



15 [000124] Compound V is a ligand for AR with potent binding affinity, exhibits tissue-selective androgenic and anabolic effects, and is orally bioavailable. Compound V is a powerful anabolic agent that maintains the mass of the levator ani in castrated male rats.

20 [000125] Myosin heavy chain (MHC) is the predominant protein in skeletal muscle encoded by a multigene family expressed in a tissue-specific and developmentally regulated manner [Adams G.R., Zeng S.A., Baldwin K.M. *Am. J. Physiol.* 276:R954-R961, 1999]. To further demonstrate the importance of compound V in muscle, the effects of this nonsteroidal anabolic agent directly in skeletal muscle by monitoring 25 the expression of MHC subtypes using RT-PCR has been demonstrated. In steady state, mRNA expression usually parallels the pattern of MHC protein expression. Because transcription of MHC mRNA occurs in advance of MHC protein translation, and the increased sensitivity of RT-PCR compared to western blotting, rapid changes in mRNA expression can be detected and used to analyze the subtle

dynamic effects of muscle anabolism [Wright C., Haddad F., Qin A. X., Baldwin K.M. *J. Appl. Phys.* 83 (4):1389-1396, 1997].

Methods:

5 [000126] Rat muscle tissue was harvested in 5 volumes of RNA later solution (Ambion, cat.# 7020) and stored at 4°C until used for RNA isolation. Total RNA was isolated in the FastPrep FP120 instrument (Qbiogene) using RNAqueous-4PCR kit (Ambion, cat # 1914) in combination with FastRNA green tubes (Qbiogene, cat.# 6040-600) at settings for time at 45 sec and speed at 6.5. 1 ug of total RNA was
10 used for reverse transcription using Retroscrip kit (Ambion, cat# 1710). The mixture was incubated at 42 °C for 60 min, followed by 10 min at 92 °C, and then chilled on ice and used in PCR reaction.

15 [000127] Relatively quantitative RT-PCR was used to analyze expression of MHC mRNA in rat *musculus masseter* (MM) and *levator ani* (LA). As an internal standard 18S ribosomal RNA was used (QuantumRNA classic 18S Internal Standard, Ambion, cat.# 1716). Linear range of PCR reaction for all primers as well as optimal ratio of 18S primers to competitors to achieve the same level of amplification as the genes of interest was determined.

20 [000128] Primers were obtained from IDT based on the recently published design (Wright et al., *J. Appl. Phys.* 1997;83:1389), with the following sequence: 5'GAAGGCCAAGAAGGCCATC3'.

25 [000129] To design a perfect match of upstream primers for the neonatal sequence, slight modifications of the above common primer was necessary (Table1). The optimal annealing temperature of these degenerate common primers was, however, unchanged, and they were used in the same manner as the common primer as 5'-oligonucleotides for PCR reactions. The 3'-oligonucleotides used in the
30 PCR reactions were designed from the 3'-untranslated regions of each of the

different MHC genes, where the sequences are highly specific for each MHC gene [Wright et al 1997]:

5 Table 1. *Oligonucleotide primers used for PCR amplification reactions*

MHC subtype	Common Primer	Antisense Primer
IIb	5'GAAGGCCAAGAAGGCCATC3'	5'GTGTGATTCTTCTGTCACC3'
IIx	5'GAAGGCCAAGAAGGCCATC3'	5'GGTCACCTTCCTGCTTGG3'
neonatal	5'GAAGGCCAAGAAGGCCATC3'	5'GCGCCCTCCTCAAGATGCGT3'

[000130] 5 units of Taq DNA polymerase (Roche, cat# 1146165), 200 μ M of each dNTP (Invitrogen, cat.#R725-01), 0.2 μ M each MHC primer (IDT), 1 μ l of cDNA from reverse transcription reaction and 4 μ l of 18S primers : competitors mixture 10 were used in 50 μ l PCR reaction. Amplification was carried out in PTC-100 Programmable Thermal Controller (MJ Research, Inc.) with an initial denaturation step of 3 min at 94 °C, followed by optimized number of cycles for the MHC primer pair, with each cycle consisting of 45 sec at 94 °C, 60 sec at 48 °C, 90 sec 72 °C, and a final step of 5 min at 72 °C. PCR products were analyzed by agarose gel 15 electrophoresis [20- μ l aliquots of a 50- μ l PCR reaction loaded on a 1.5% agarose gel (in 1x Tris-Acetate-EDTA buffer) containing 0.2 μ g/ml ethidium bromide] to visualize the PCR products. Gels were photographed under ultraviolet (UV) light using Polaroid instant film number 57 to generate an image of the gel. Pictures were scanned and the volume of the optical density (OD) of a DNA band was 20 determined by the Image Quant software (Molecular Dynamics), and the background was subtracted (so local background was directly proportional to the amount of DNA over a wide range). Intensity (volume of the OD) of the MHC band was divided by the intensity of the control fragment, thereby correcting for any 25 differences in the efficiency of the PCR reactions. The content of each experimental group MHC gene was calculated as a percentage of the MHC value in the control group (Table 2).

Results:

[000131] The masseter muscle dissected from untreated intact female rats was set as the control level (representing 100%) of MHC IIb expression (see histogram in Figure 1a). Intact female rats treated with androgens were evaluated against the 5 untreated controls for the effect of treatment on MHC IIb from masseter. The results indicate that testosterone propionate has a positive effect on masseter muscle where it increased transcription of MCH type IIb to 142% of untreated control (Figure 1b). Compound V was found to have a similar effect where it increased level of MHC IIb transcript to 124% (Figure 1b). Actual untransformed 10 data (PCR results) is shown in Figure 1a.

In these same rats, the levator ani was dissected and evaluated for the expression pattern of MHC family members. The data indicate that all animals treated with androgens (TP or Compound V) for a period of 14- and 28-days had a 15 muscle present in the location expected for the levator ani, and further characterization of this tissue by RT-PCR demonstrates presence of MHC type IIb and very little expression of MHC subtypes IIx and the neonatal isoform. The SDS-PAGE as well as immunoblotting with a MHC type II specific antibody revealed a single band of apparent molecular weight of about 200 kDa. These results are 20 consistent with the presence of a levator ani muscle [Talmadge R. J. and Roy R.R. *J. Appl. Physiol.* 75(5): 2337-2340, 1993].

Table 2. Intensity of the bands resolved on agarose gel expressed as average intensity of all pixels in the spot.

Treatment	18 S	II b	II b / 18 S	%
Control	102	46	0.45	100
TP	141	90	0.64	141.5
Compound V	171	96	0.56	124.5

25

[000132] In a similar experiment with masseter muscle and gastrocnemius muscle, the masseter and gastrocnemius muscles dissected from untreated intact male rats were set as the control level (representing 100%) of MHC IIb expression (Figure 2).

Intact male rats treated with androgens were evaluated against the untreated controls for the effect of treatment on MHC IIb from masseter or gastrocnemius. The results indicate that testosterone propionate has a positive effect on masseter muscle where it increased transcription of MHC type IIb to 120(±14)% of untreated 5 control (Figure 2 - Top). Compound V was also anabolic in muscle, with an increase in MHC type IIb to 117(±13)% (Figure 2 - Top). In gastrocnemius muscle, similar results were observed. Testosterone propionate has a positive effect on gastrocnemius muscle where it increased transcription of MHC type IIb to 139(±47)% of untreated control (Figure 2 - Bottom). Compound V was also 10 anabolic in muscle, with an increase in MHC type IIb to 162(±54)% (Figure 2 - Bottom).

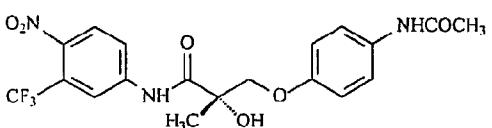
Conclusions:

[000133] These results demonstrate that both the selective androgen receptor 15 modulator (SARM) as exemplified by compound V and TP have direct anabolic effects on the musculoskeletal system in intact female and male rats as measured by a net increase in the expression of mRNA for MHC. Additionally, treatment with these anabolic agents for a period of 14- and 28-days resulted in muscular hypertrophy of the levator ani. Testosterone has been recognized as an anabolic 20 androgen for several decades. It has been demonstrated herein, that the selective androgen receptor modulator (SARM) as exemplified by Compound V is an orally bioavailable nonsteroidal agent with tissue selective anabolic effects in male rats and which increases muscle mass. The selective androgen receptor modulator (SARM) as described hereinabove, may be used to treat among other diseases or 25 conditions catabolic syndromes of sarcopenia associated with aging or chronic illness, and sexual dysfunction in females.

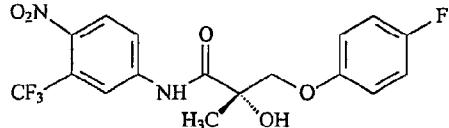
EXAMPLE 2**Pharmacologic Activity and Tissue-Selectivity of Compounds V and VI in Rats of Varying Hormonal Status**

5 [000134] Previous studies by Applicants demonstrated that Compound V is a potent and efficacious selective androgen receptor modulator (SARM) in castrated male rats. To provide a representative model of the vast majority of men that will eventually receive this drug, Applicants completed a preclinical study to compare the pharmacologic effects and tissue-selectivity of Compound V, Compound VI –
 10 another potent SARM, and testosterone propionate (TP) in male rats of varying hormonal status. Male rats with normal testicular function (i.e., intact with no surgical manipulation) were included to examine the effects of Compound V on animals with normal blood levels of testosterone. Male rats that received unilateral orchidectomy (i.e., surgical removal of one testis) were included to examine the effects of Compound V on animals with slight androgen depletion. Male rats that received bilateral orchidectomy (i.e., surgical removal of both testes) were included
 15 to examine the effects of Compounds V and VI on androgen-deficient animals.

20



V



VI

Methods:

[000135] Compounds V and VI were synthesized and characterized in the laboratory of Dr. Duane Miller at the University of Tennessee, Memphis, TN. Male Sprague-Dawley rats were purchased from Harlan Biosciences (Indianapolis, IN). The animals were maintained on a 12-h cycle of light and dark with food and water available *ad libitum*. All animal studies were reviewed and approved by the Animal Care and Use Committee of The Ohio State University, and conformed to the Principles of Laboratory Animal Care (NIH publication #85-23, revised 1985).
 25 30 Immature male Sprague-Dawley rats weighing 187 to 214 g were randomly distributed into 9 groups of 5 animals. One day before the initiation of drug

treatment, groups 4 through 6 and groups 7 through 9 received unilateral or bilateral orchidectomy, respectively, via a midline scrotal incision. Groups 1 through 3 did not undergo surgery. All drugs given to animals were freshly prepared as solutions in polyethylene glycol 300 (PEG 300). Groups 4 and 7 received treatment 5 with vehicle alone (i.e., PEG 300). Animals in groups 3, 6, and 9 received testosterone propionate (TP, 0.5 mg/day) via implantation of subdermal osmotic pumps (Model 2002, Durect Corporation, Palo Alto, CA). Animals in groups 2, 5, and 8 received Compound V or Compound VI (0.5 mg/day) via implantation of 10 subdermal osmotic pumps. After 14 days of drug treatment, rats were weighed, anesthetized, and sacrificed. The ventral prostates, seminal vesicles, and levator 15 ani muscle were removed and weighed. Osmotic pumps were also removed from animals to check for correct pump operation. The weights of all organs were normalized to body weight, and analyzed for any statistically significant differences between groups using single-factor ANOVA with the alpha value set *a priori* at $p < 0.05$. The weights of prostates and seminal vesicles were used as indices for 20 evaluation of androgenic activity, and the levator ani muscle weight was used to evaluate the anabolic activity. Statistical analyses of parameters from complete blood count or serum chemical profiling, wherever applicable, were performed by single-factor ANOVA with the alpha value set *a priori* at $p < 0.05$.

20

Results:

[000136] As shown in Table 3 and Figure 3, in intact animals, Compound V decreased the size of the prostate to 79% and, of that observed in control animals 25 (Fig 3A), with no statistically significant changes in the size of the seminal vesicles (Fig 3B) or levator ani muscle (Fig 3C). The pharmacologic effects and tissue selectivity of Compound V were more obvious in hemi-orchidectomized animals (Table 3 and Figure 4). Compound V decreased the size of the prostate (Fig 4A) and seminal vesicles (Fig 4B) to 75% and 79%, respectively, and increased the size of the levator ani muscle (Fig 4C) to 108% of that observed in untreated hemi- 30 orchidectomized animals. These observations demonstrate that Compound V acts as a partial agonist in prostate and seminal vesicles and as a full agonist in levator ani muscle. No adverse pharmacologic effects were observed. Similarly, as

shown in Table 3 and in Figures 5 and 6, in castrated animals.

[000137] **Table 3. Comparison of androgenic and anabolic effects of Compound V and TP on intact, hemi-orchidectomized and castrated rats (% of intact control, n=5).**

Organ		Control	Compound V (0.5 mg/day)	TP (0.5 mg/day)
Prostate	Intact	100.00 ± 13.13	79.41 ± 9.32*†	97.45 ± 10.82
	Hemi-	86.42 ± 19.52	74.69 ± 8.44*†	98.57 ± 7.98
	Castrated	7.19 ± 1.25	32.55 ± 11.65*‡	76.78 ± 10.43*‡
Seminal Vesicle	Intact	100.00 ± 18.84	90.54 ± 12.10	103.95 ± 13.23
	Hemi-	102.93 ± 7.47	78.55 ± 13.58*‡	114.19 ± 23.81
	Castrated	8.97 ± 1.23	16.47 ± 5.21*‡	63.48 ± 17.05*‡
Levator Ani	Intact	100.00 ± 12.69	109.15 ± 14.68	95.61 ± 9.34
	Hemi-	92.94 ± 7.83	108.10 ± 8.92*‡	98.63 ± 10.47
	Castrated	42.74 ± 5.22	100.65 ± 10.86*‡	87.27 ± 10.25*‡

* p<0.05 compared to intact control group.

† p<0.05 compared to TP of same surgical status (i.e., intact, hemi-orchidectomized, or castrate).

‡ p<0.05 compared to control group of same surgical status.

10

[000138] A comparison of the androgenic and anabolic activities of Compound V and Compound VI is provided in Table 4.

15

Table 4:

**Table 4 Comparison of Androgenic and Anabolic Activities of Compounds VI and V
TO TP**

	Organ	Treatment	E _{max} (% of Intact Control)	Relative Affinity	ED ₅₀ (mg/day)	Relative Potency
Androgenic	Prostate	TP	120.6 ± 13.4	1.00	0.13 ± 0.03	1.00
		Compound VI	14.5 ± 0.7	0.12	0.42 ± 0.04	0.31
		Compound V	35.2 ± 0.4	0.29	0.43 ± 0.01	0.30
Anabolic	Seminal Vesicle	TP	70.0 ± 18.8	1.00	0.12 ± 0.02	1.00
		Compound VI	12.7 ± 3.1	0.18	0.38 ± 0.26	0.32
		Compound V	28.5 ± 0.8	0.40	0.55 ± 0.02	0.22
Anabolic	Levator Ani	TP	104.2 ± 10.1	1.00	0.15 ± 0.03	1.00
	Muscle	Compound VI	74.9 ± 0.4	0.72	0.44 ± 0.01	0.34
		Compound V	101.0 ± 1.0	0.97	0.14 ± 0.01	1.07

Conclusions:

[000139] Compound V demonstrated potent and tissue-selective pharmacologic effects in intact, hemi-orchidectomized and castrated male rats. Compound V led to significant decreases in prostate weights in intact and hemi-orchidectomized animals, and was less effective than TP at increasing the weight of the prostate in castrated animals. Similar pharmacologic effects were noted in the seminal vesicles (another organ generally considered as a marker of androgenic effects), with the exception that Compound V had no effect on the weight of the seminal vesicles in intact animals. Compound V treatment led to significant increases in the weight of the levator ani muscle in hemi-orchidectomized and castrated animals. These effects were greater than those observed with TP. These data demonstrate the tissue-selective pharmacologic effects of Compound V. It is important to note that these effects were observed in the absence of any significant changes in plasma concentrations of FSH, LH and testosterone (not shown). In summary, these data show that Compound V elicits an optimal pharmacological profile in male animals, identifying it as the first member of a new class of orally bioavailable and tissue-selective SARMs.

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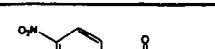
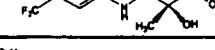
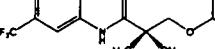
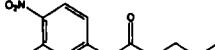
EXAMPLE 3**Pharmacologic Activity and Tissue-Selectivity of selected halogenated Selective Androgen Receptor Modulators in Rats**

[000140] Compounds VI-X in Table 5 were synthesized and characterized in the 30 laboratory of Dr. Duane Miller at the University of Tennessee, Memphis, TN.

[000141] The tissue-selectivity and pharmacologic effects of Compounds VI-X were determined as described above in Example 2.

[000142] Table 5 shows the chemical structures and binding affinities of Compounds VI-IX. Binding affinities were determined as described in He et al. *Eur. J. Med. Chem.* (2002), 619-634; and as described in Mukherjee et al. *Xenobiotica* (1996), 26, 117-122.

Table 5:

Compound Name	Structure	Molecular weight	RBA (%)	Ki (nM)
VI		402	26.4	2.3±0.06
VII		419	7.6	8.6±1.2
VIII		462	5.3	12.6±1.8
IX		510	2.7	23±1.6

10 Results:

[000143] As shown in Figure 7, Compounds VI-IX demonstrated tissue-selective pharmacological effects in castrated male rats, with higher efficacy in anabolic tissues (i.e. levator ani) as compared to androgenic tissues (i.e. prostate and seminal vesicles). Compounds VI-IX all had an anabolic effect, increasing the weight of the levator ani muscle in a dose-dependent manner. Compounds VI, VIII and IX (Figures 7 A, C and D, respectively) increased the weight of the levator ani muscle to values close to those of the intact controls. The effect of compound VII (Figure 7B) was even more pronounced – increasing the weight of the levator ani muscle to values exceeding those of intact controls. There were no statistically significant changes in the sizes of the prostate or seminal vesicles. These data demonstrate the tissue-selective pharmacologic effects of Compounds VI-IX.

EXAMPLE 4**Pharmacologic Activity and Tissue-Selectivity of Compound X in Rats**

[000144] Compound X (Table 6) was synthesized and characterized in the laboratory
5 of Dr. Duane Miller at the University of Tennessee, Memphis, TN.

[000145] The tissue-selectivity and pharmacologic effects of Compound X were
determined as described above in Examples 2 and 3.
10 [000146] Table 6 shows the chemical structure and binding affinity of Compound X.
Binding affinities were determined as described in He et al. .

Table 6:

Compound Name	Structure	Molecular weight	Ki (nM)
X		382.3	3.3 ± 0.08

15 Results:

[000147] As shown in Table 7 and Figure 8, Compound X demonstrated tissue-selective pharmacological effects in castrated male rats, with higher efficacy in anabolic tissues (i.e. levator ani) as compared to androgenic tissues (i.e. prostate and seminal vesicles). Compound X demonstrated little pharmacologic activity in
20 the prostate (8.7 ± 1.39% of intact at 1.0 mg/day dose) and seminal vesicles (10.7 ± 0.91% of intact at 1.0 mg/day dose), suggesting that it acts as a weak partial agonist in these tissues. Importantly, Compound X demonstrates highly efficacious anabolic activity at 1.0 mg/day dose, returning the levator ani muscle to 75.2 ± 9.51% of that observed in intact animals.

25

30

TABLE 7. Average (Mean \pm S.D.) Organ Weights

	Prostate	Levator Ani	Seminal Vesicles
Intact Control	100 \pm 11.28	100 \pm 12.12	100 \pm 2.48
Castrated Control	7.6 \pm 0.68	45.9 \pm 10.84	8.4 \pm 1.05
0.10 mg/day	6.4 \pm 0.82	54.9 \pm 5.77	8.8 \pm 1.18
0.25 mg/day	5.7 \pm 0.61	61.0 \pm 5.23	7.6 \pm 1.37
0.50 mg/day	6.2 \pm 0.56	55.0 \pm 9.23	9.3 \pm 1.57
0.75 mg/day	7.6 \pm 0.74	68.9 \pm 8.46	9.8 \pm 3.65
1.00 mg/day	8.7 \pm 1.39	75.2 \pm 9.51	10.7 \pm 0.91

5

EXAMPLE 5**Pharmacologic Activity and Tissue-Selectivity of Compounds XI and XII in Rats**

[000148] Compounds XI and XII (Table 8) was synthesized and characterized in the 10 laboratory of Dr. Duane Miller at the University of Tennessee, Memphis, TN.

[000149] The tissue-selectivity and pharmacologic effects of Compounds XI and XII were determined as described above in Examples 2-4.

15 [000150] Table 8 shows the chemical structure and binding affinity of Compounds XI and XII. Binding affinities were determined as described in He et al.

Table 8:

Compound Name	Molecular Weight	Structure	Ki (nM)	RBA (%)
XI	C ₁₇ H ₁₃ F ₅ N ₂ O ₅ 420.29		3.4 \pm 0.56	17.6
XII	C ₁₇ H ₁₀ F ₈ N ₂ O ₅ 474.26		1.37 \pm 0.34	13.3

20

Results:

[000151] As shown in Table 9 and Figure 9, Compounds XI and XII demonstrated

tissue-selective pharmacological effects in castrated male rats, with higher efficacy in anabolic tissues (i.e. levator ani) as compared to androgenic tissues (i.e. prostate and seminal vesicles). Compound XI demonstrated partial pharmacologic activity in the prostate ($33.1 \pm 8.5\%$ of intact at 1.0 mg/day dose after injection) and 5 seminal vesicles ($23.6 \pm 8.8\%$ of intact at 1.0 mg/day dose after injection), suggesting that it acts as a weak partial agonist in these tissues. Importantly, Compound XII demonstrated highly efficacious anabolic activity at 1.0 mg/day dose, returning the levator ani muscle to $112.8 \pm 9.4\%$ of that observed in intact 10 animals (daily injection), and $122.5 \pm 10.4\%$ of that observed in intact animals (pump). Compound XII demonstrated little pharmacologic activity in the prostate ($7.2 \pm 1.4\%$ of intact at 1.0 mg/day dose) and seminal vesicles ($7.2 \pm 0.9\%$ of intact at 1.0 mg/day dose), suggesting that it acts as a weak partial agonist in these tissues. Importantly, Compound XII demonstrated anabolic activity at 1.0 mg/day dose, returning the levator ani muscle to $55.83 \pm 2.84\%$ of that observed in intact 15 animals.

Table 9:

	Intact	Castrated	XI (pump)	XI (daily injection)	XII (daily injection)
Prostate	100 ± 14.3	6.2 ± 2.5	40.3 ± 10.0	33.1 ± 8.5	7.2 ± 1.4
Seminal Vesicles	101 ± 26.8	8.1 ± 1.8	30.9 ± 5.7	23.6 ± 8.8	7.2 ± 0.9
Levator Ani Muscle	102 ± 8.1	40.9 ± 9.4	122.5 ± 10.4	112.8 ± 9.4	55.83 ± 2.84

20 * Reference group that treated with GTx02-CK2-1 1 mg/day via osmotic pump.

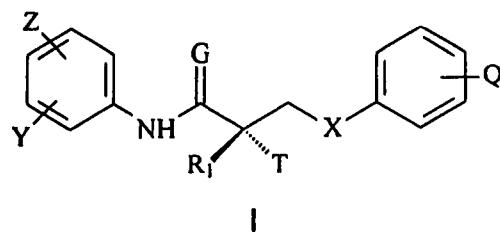
[000152] It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims which follow:

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, ie. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be clearly understood that although prior art publication(s) are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art in Australia or in any other country.

WHAT IS CLAIMED IS:

1. A method of (a) treating a subject suffering from a muscle wasting disorder (b) preventing, suppressing, inhibiting or reducing the incidence of a muscle wasting disorder in a subject (c) treating, preventing, suppressing, inhibiting or reducing muscle loss in a subject suffering from a muscle wasting disorder (d) treating, preventing, inhibiting, reducing or suppressing muscle wasting in a subject suffering from a muscle wasting disorder or (e) treating, preventing, inhibiting, reducing or suppressing muscle protein catabolism in a subject suffering from a muscle wasting disorder, comprising the step of administering to said subject a selective androgen modulator (SARM) compound.
2. The method of claim 1, wherein said method comprises administering an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of said SARM compound, or any combination thereof.
3. The method according to claim 1, wherein said SARM compound is represented by the structure of formula I:



wherein

G is O or S;

X is a bond, O, CH₂, NH, Se, PR, NO or NR;

T is OH, OR, -NHCOCH₃, or NHCOR

Z is NO₂, CN, COOH, COR, NHCOR or CONHR;

Y is CF₃, F, I, Br, Cl, CN, C(R)₃ or Sn(R)₃;

Q is alkyl, halogen, CF₃, CN, C(R)₃, Sn(R)₃, N(R)₂, NHCOCH₃,

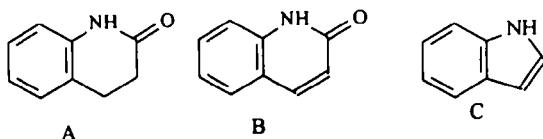
NHCOCF₃, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR,

NHCSCH₃, NHCSCF₃, NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR,

OCOR, OSO₂R, SO₂R, SR; or Q together with the benzene ring to

which it is attached is a fused ring system represented by structure A,

B or C:

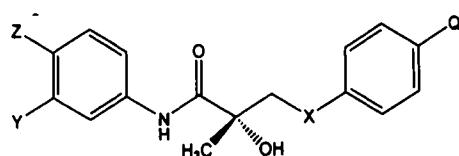


R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃,

CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH; and

R₁ is CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, or CF₂CF₃.

4. The method according to claim 1, wherein said SARM compound is represented by the structure of formula II.



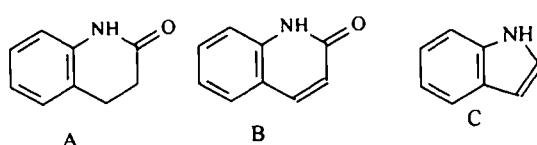
II

wherein X is a bond, O, CH₂, NH, Se, PR, NO or NR;

Z is NO₂, CN, COOH, COR, NHCOR or CONHR;

Y is CF₃, F, I, Br, Cl, CN, C(R)₃ or Sn(R)₃;

Q is alkyl, halogen, CF₃, CN, C(R)₃, Sn(R)₃, N(R)₂, NHCOCH₃, NHCOCF₃, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, NHCSCH₃, NHCSCF₃, NHCSR, NHSO₂CH₃, NHSO₂R, OR, COR, OCOR, OSO₂R, SO₂R, SR; or Q together with the benzene ring to which it is attached is a fused ring system represented by structure A, B or C:



R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃, CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH.

5. The method according to claim 4, wherein X is O.

6. The method according to claim 4, wherein Y is CF₃.

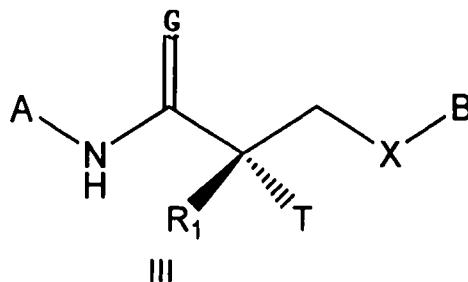
7. The method according to claim 4, wherein Z is NO₂.

8. The method according to claim 4, wherein Z is CN.

9. The method according to claim 4, wherein Q is halogen.

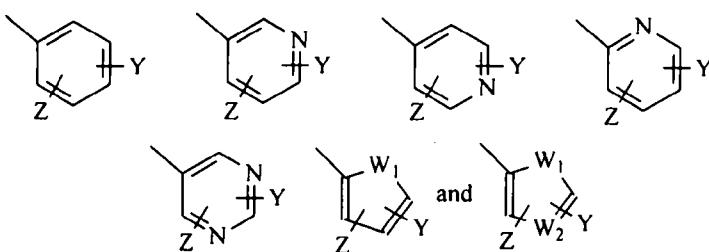
10. The method according to claim 4, wherein Q is NHCOCH₃.

11. The method according to claim 4, wherein X is O, Z is NO₂, Y is CF₃ and Q is halogen.
12. The method according to claim 4, wherein X is O, Z is NO₂, Y is CF₃ and Q is NHCOCH₃.
13. The method according to claim 4, wherein X is O, Z is CN, Y is CF₃ and Q is halogen.
14. The method according to claim 4, wherein X is O, Z is CN, Y is CF₃ and Q is NHCOCH₃.
15. The method according to claim 1, wherein said SARM compound is represented by the structure of formula III.

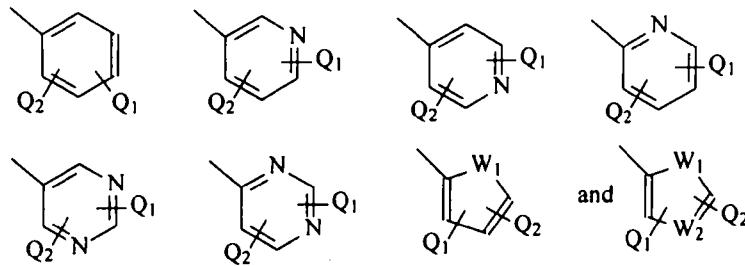


wherein X is a bond, O, CH₂, NH, Se, PR, NO or NR;
 G is O or S;
 R₁ is CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, or CF₂CF₃;
 T is OH, OR, -NHCOCH₃, or NHCOR;
 R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH₂F, CHF₂, CF₃,
 CF₂CF₃, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:

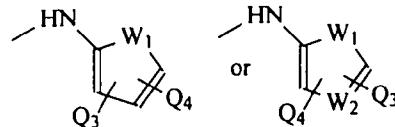


wherein A and B cannot simultaneously be a benzene ring;

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

Y is CF_3 , F , I , Br , Cl , CN , $\text{C}(\text{R})_3$ or $\text{Sn}(\text{R})_3$;

Q_1 and Q_2 are independently of each other a hydrogen, alkyl, halogen, CF_3 , CN , $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, 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 ,

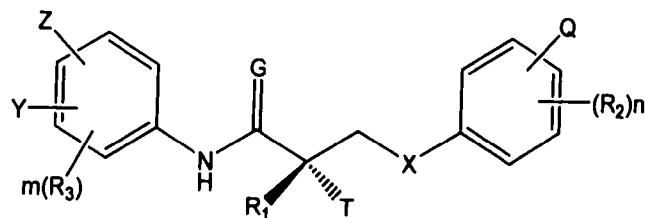


Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3 , CN , $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$, NHCOCH_3 , NHCOCF_3 , NHCOR , NHCONHR , NHCOOR , OCONHR , CONHR , NHCSCH_3 , NHCSCF_3 , NHCSR , NHSO_2CH_3 , NHSO_2R , OR , COR , OCOR , OSO_2R , SO_2R or SR ;

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

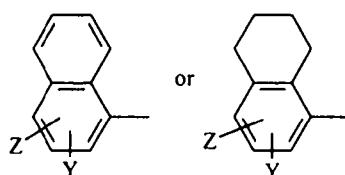
W_2 is N or NO.

16. The method according to claim 1, wherein said SARM compound is represented by the structure of formula IV:

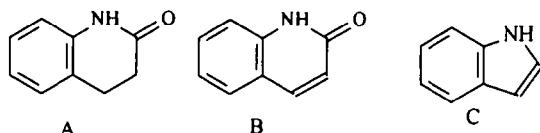


IV

wherein X is a bond, O, CH_2 , NH, Se, PR, NO or NR;
 G is O or S;
 T is OH, OR, $-\text{NHCOCH}_3$, 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 , $\text{N}(\text{R})_2$, SR;
 R_3 is F, Cl, Br, I, CN, NO_2 , COR, COOH, CONHR, CF_3 , $\text{Sn}(\text{R})_3$,
 or R_3 together with the benzene ring to which it is attached forms a
 fused ring system represented by the structure:



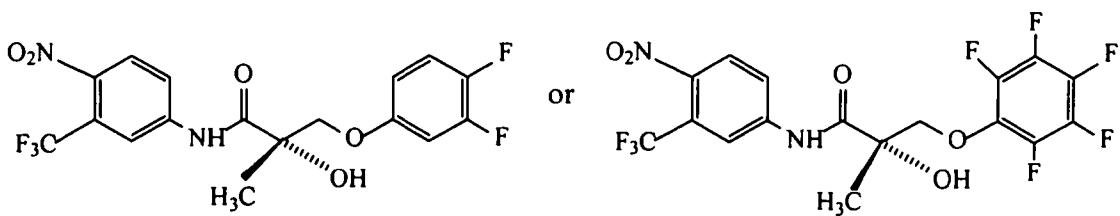
Z is NO_2 , CN, COR, COOH, or CONHR;
 Y is CF_3 , F, Br, Cl, I, CN, or $\text{Sn}(\text{R})_3$;
 Q is H, alkyl, halogen, CF_3 , CN, $\text{C}(\text{R})_3$, $\text{Sn}(\text{R})_3$, $\text{N}(\text{R})_2$,
 NHCOCH_3 , NHCOCF_3 , NHCOR , NHCONHR , NHCOOR , OCONHR ,
 CONHR , NHCSCH_3 , NHCSCF_3 , NHCSR , NHSO_2CH_3 , NHSO_2R , OH,
 OR, COR, OCOR, OSO_2R , SO_2R , SR; 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.

17. The method according to claim 1, wherein said SARM compound is represented by the structure of formula:



18. The method of claim 1, wherein said muscle wasting disorder is due to a pathology, illness, disease or condition.
19. The method of claim 18, wherein said pathology, illness, disease or condition is neurological, infectious, chronic or genetic.
20. The method of claim 18, wherein said pathology, illness, disease or condition is a Muscular Dystrophy, a Muscular Atrophy, X-linked spinal-bulbar Muscular Atrophy (SBMA), a Cachexia, malnutrition, Leprosy, Diabetes, Renal Disease, Chronic Obstructive Pulmonary Disease (COPD), Cancer, end stage Renal failure, Sarcopenia, Emphysema, Osteomalacia, HIV Infection, AIDS, or Cardiomyopathy.
21. The method according to claim 1, wherein said muscle wasting disorder is an age-associated muscle wasting disorder; a disuse deconditioning-associated muscle wasting disorder; or the muscle wasting disorder is due to chronic lower back pain; burns; central nervous system (CNS) injury or damage; peripheral nerve injury or damage; spinal cord injury or damage; chemical injury or damage; or alcoholism.
22. The method according to claim 1, wherein said muscle wasting disorder is a chronic muscle wasting disorder.
23. The method according to claim 1, wherein said administering comprises administering a pharmaceutical composition comprising said SARM and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or any combination thereof; and a pharmaceutically acceptable carrier.
24. The method according to claim 23, wherein said administering comprises intravenously, intraarterially, or intramuscularly injecting to said subject said

pharmaceutical composition in liquid form; subcutaneously implanting in said subject a pellet containing said pharmaceutical composition; orally administering to said subject said pharmaceutical composition in a liquid or solid form; or topically applying to the skin surface of said subject said pharmaceutical composition.

25. The method according to claim 23 wherein said pharmaceutical composition is a pellet, a tablet, a capsule, a solution, a suspension, an emulsion, an elixir, a gel, a cream, a suppository or a parenteral formulation.

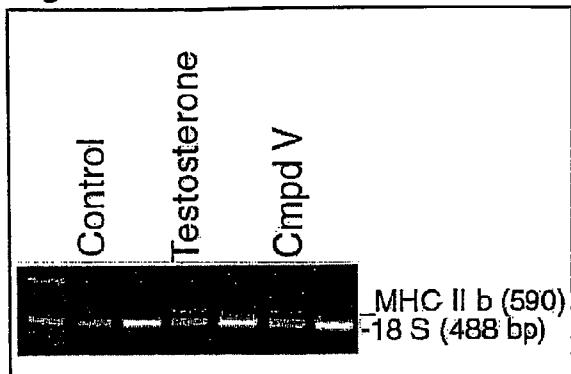
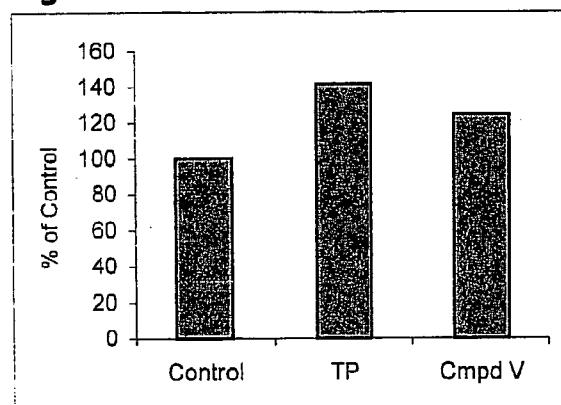
Figure 1A**Figure 1B**

Figure 2
Effects of Compound V on skeletal muscle of rat

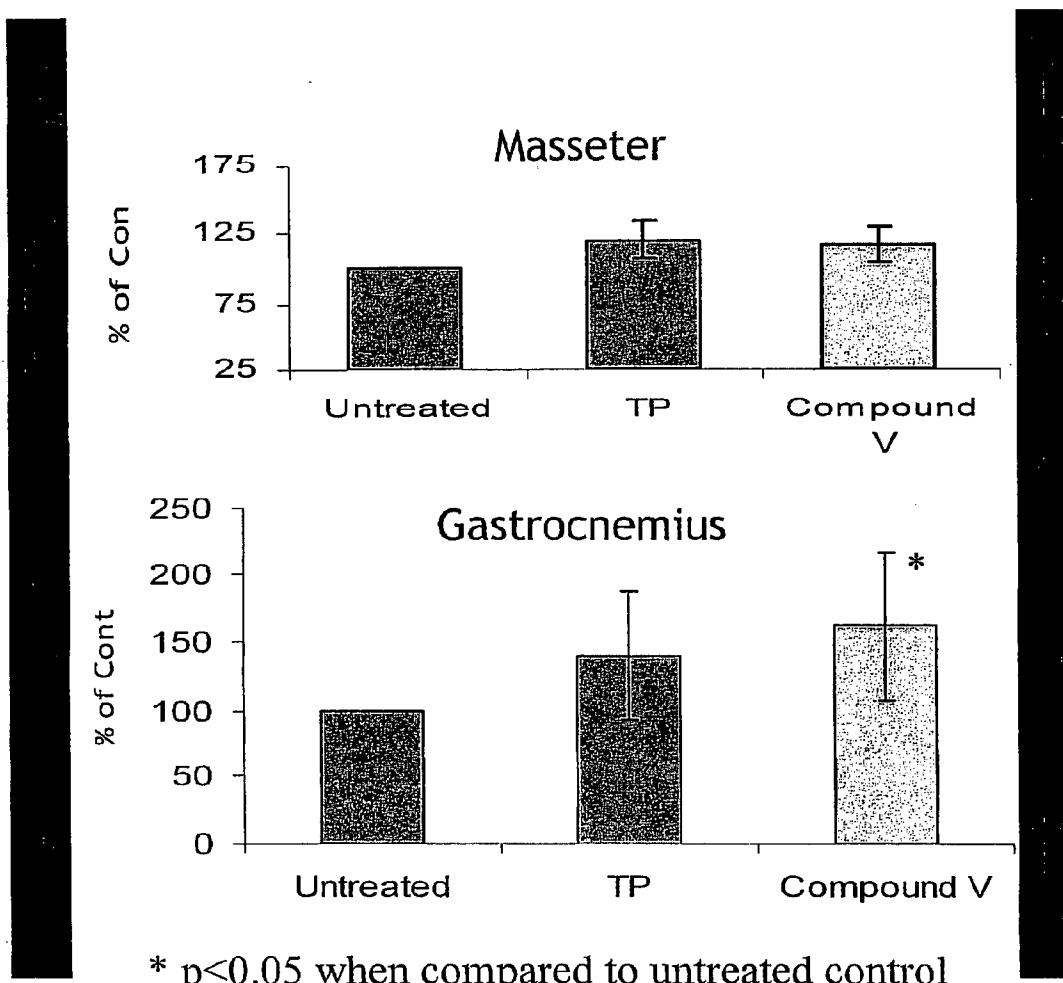
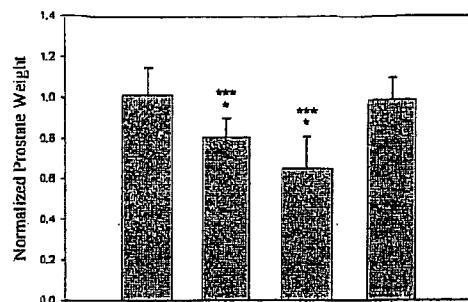
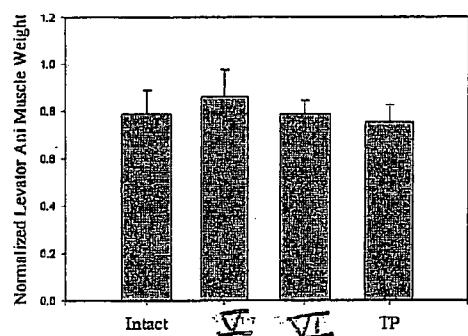


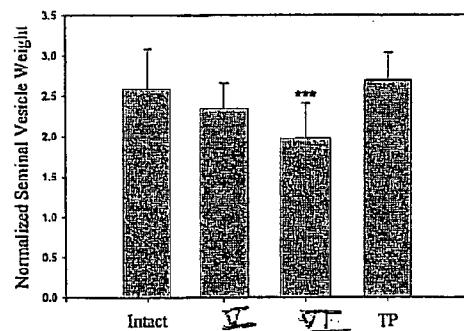
Figure 3 - Intact



A



B

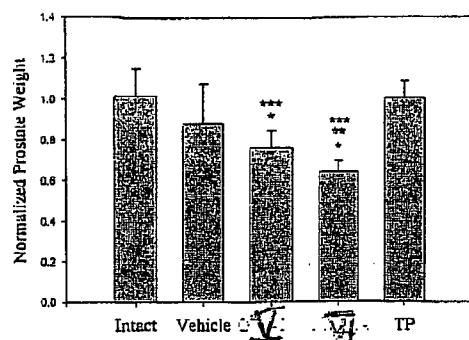


C

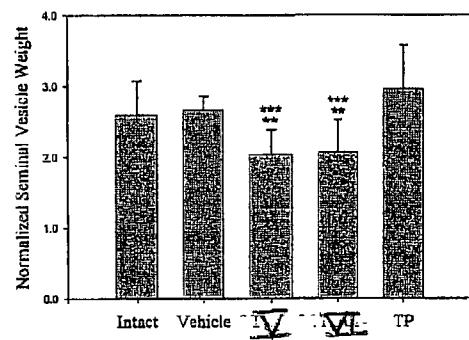
* Compared to intact control, $p < 0.05$

*** Compared to TP group, $p < 0.05$

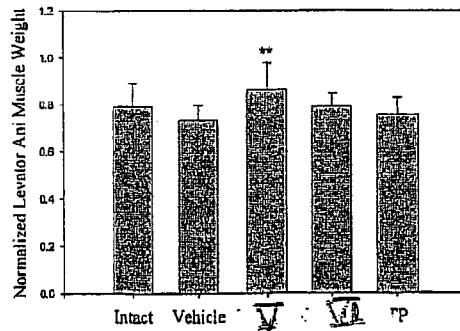
Figure 4 - Hemi-orchidectomized



A



B

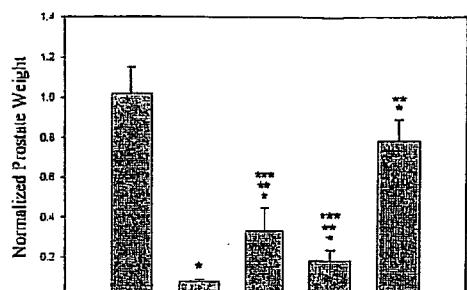
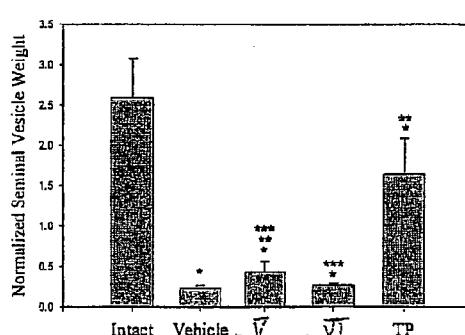
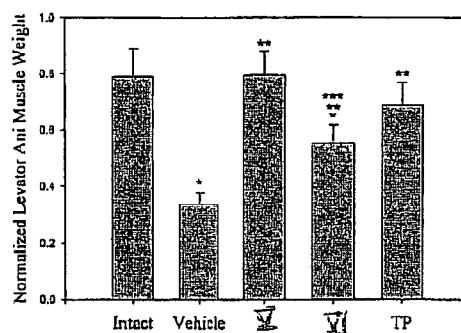


C

* Compared to intact control, $p < 0.05$

** Compared to vehicle control, $p < 0.05$

*** Compared to TP group, $p < 0.05$

Figure 5 - Castrated**A****B****C**

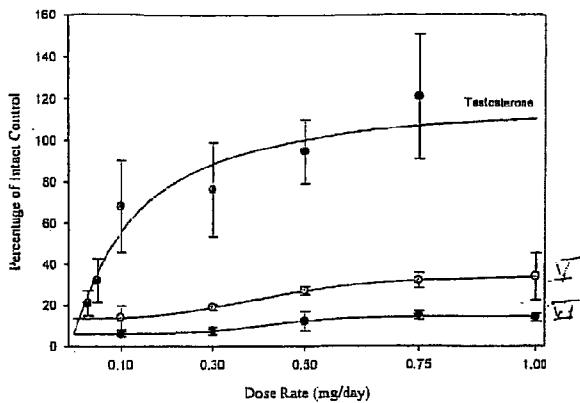
* Compared to intact control, $p < 0.05$

** Compared to vehicle control, $p < 0.05$

*** Compared to TP group, $p < 0.05$

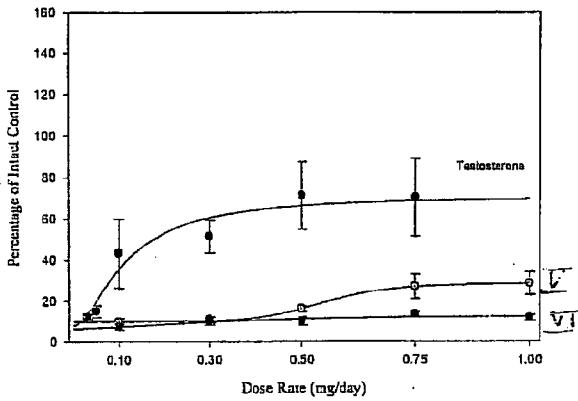
Figure 6

Prostate Dose Response Curves



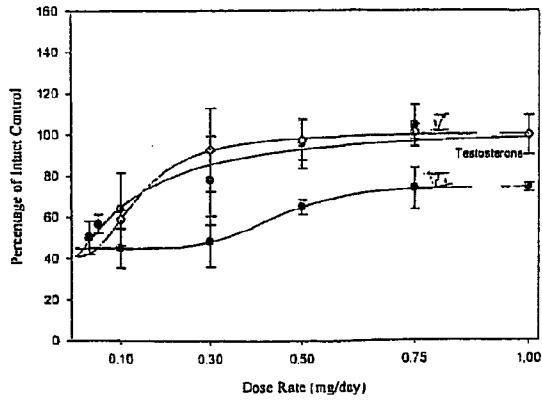
A

Seminal Vesicle Dose Response Curves



B

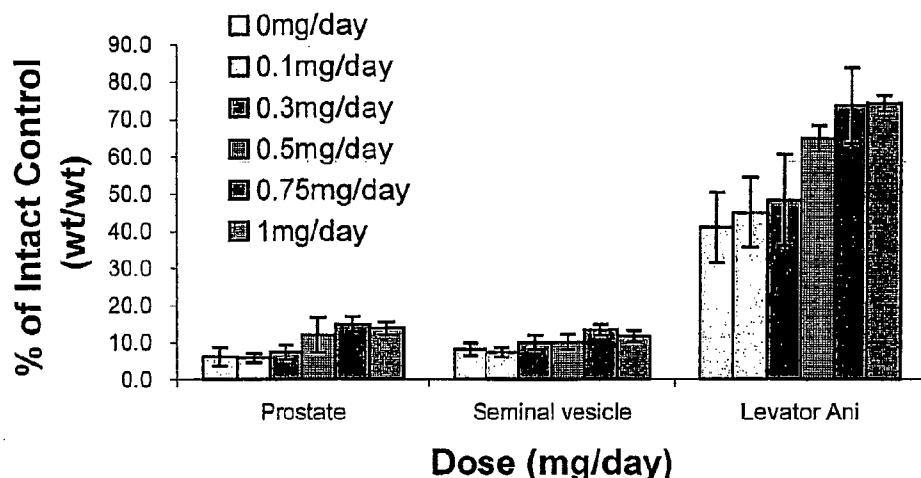
Levator Ani Muscle Dose Response Curves



C

(A)

Compound VI Pharmacology



(B)

Compound VII Pharmacology

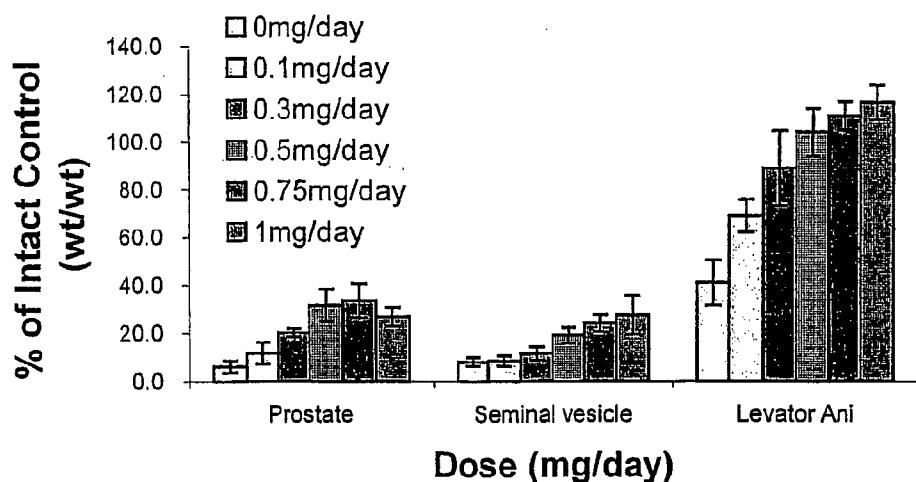
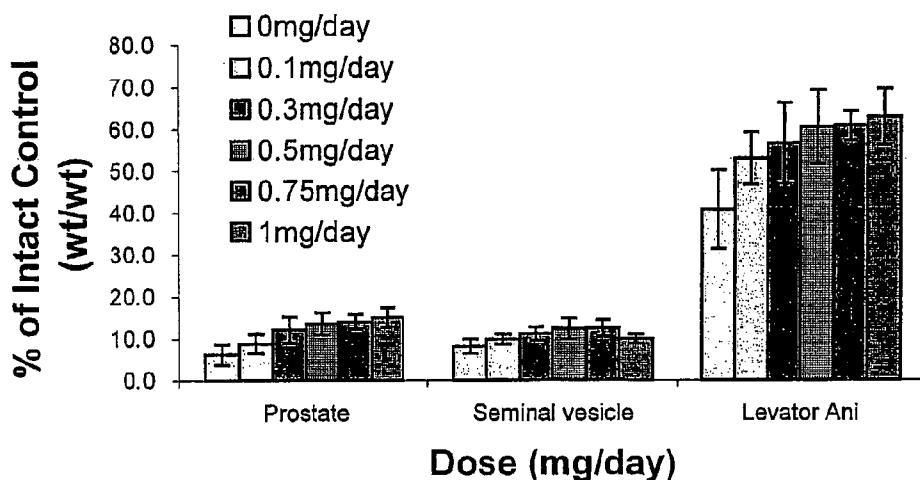


FIGURE 7 (i)

(C)

Compound VIII Pharmacology



(D)

Compound IX Pharmacology

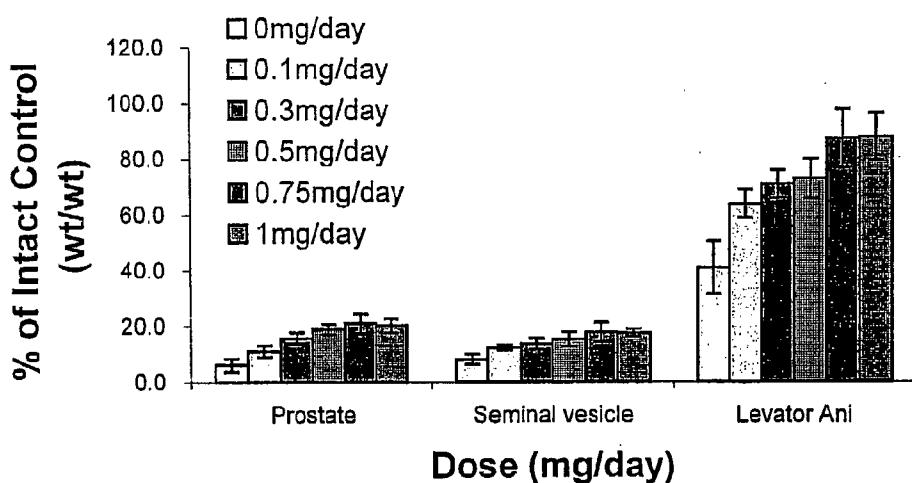


FIGURE 7 (ii)

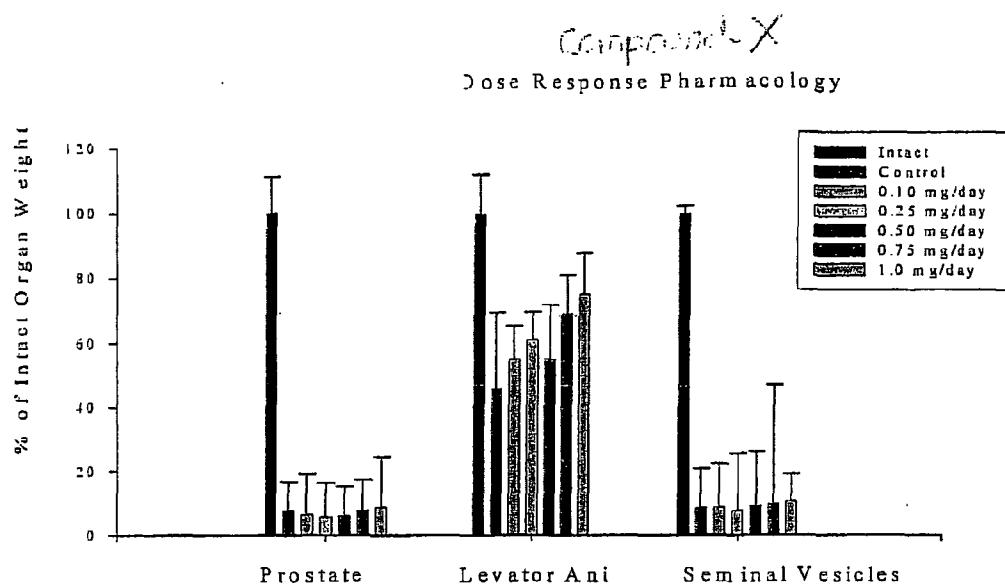


Figure 8

Organ Weights-2 week Treatment

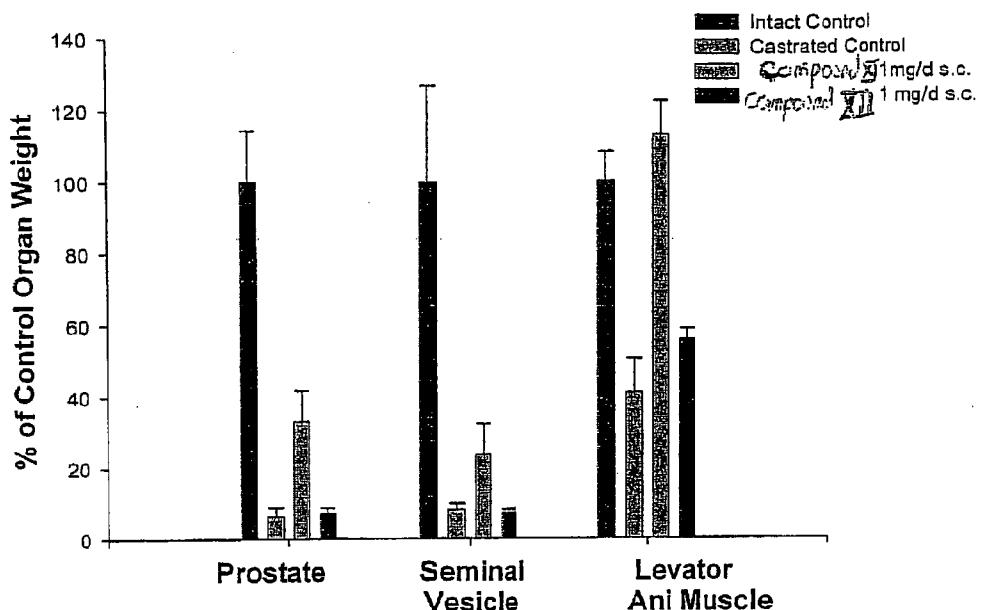


Figure 9