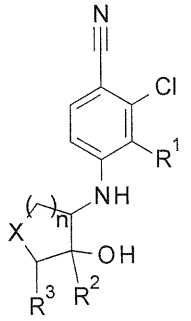
Published international patent applications, WO09/105214 and WO06/124447, disclose small molecule, non-steroidal SARMs. Still, there exists a need for new non-steroidal SARM compounds with improved potency and/or pharmacokinetic characteristics, such as exposure bioavialability. There also exists a need for efficacious SARM compounds. Additionally, there exists a need for SARM compounds that build muscle mass without the side effect of prostate gland enlargement. Androgens and SARM compounds are known to decrease HDL at efficacious exposures when delivered via oral route. Thus, there exists a need for SARM compounds that do not significantly decrease HDL levels. The present ~~invention~~disclosure provides preferred androgen receptor modulating compounds which have a minimum risk of HDL lowering at efficacious doses when delivered via a transdermal route.

Therefore, the present ~~invention~~disclosure provides novel compounds which are AR agonists. More preferably, the compounds are SARMs. Such new compounds could address the need for potent, effective treatment of muscle atrophy, hypogonadism, or cachexia with minimum risk of prostate enlargement or HDL lowering.

~~The present invention provides~~In a first aspect, there is provided a compound of formula:



wherein

n is 1 or 2;

X is $-CH_2-$ or $-O-$;

R^1 is $-CH_3$ or $-CH_2CH_3$;

R^2 is $-H$ or $-CH_3$;

R^3 is $-H$ or $-OH$;

wherein R^3 is $-H$ when X is $-O-$;

or a pharmaceutically acceptable salt thereof.

The present ~~invention~~disclosure further provides a method for the treatment or prevention of muscle atrophy in a patient comprising administering to a patient in need of such treatment or prevention an effective amount of a compound ~~of the present invention~~as defined above, or a pharmaceutically acceptable salt thereof. In a particular aspect, the present ~~invention~~disclosure provides a method of treating or preventing muscle atrophy associated with disuse, trauma, immobilization, spinal cord injury, or stroke comprising administering to a patient in need thereof an effective amount of a compound as defined above~~of the present invention~~. Even more particularly, the present ~~invention~~disclosure provides a method of treating or preventing muscle atrophy associated with hip or knee replacement, hip fracture, spinal cord injury, or stroke comprising administering to a patient in need thereof an effective amount of a compound of the present ~~invention~~disclosure.

Additionally, the present ~~invention~~disclosure provides a pharmaceutical formulation comprising a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

In a second aspect, there is provided~~The present invention provides~~ a pharmaceutical composition comprising a compound ~~of the invention~~as defined above, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. In a further embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solvate, wherein the solvate molecules include ethanol and isopropanol. In a further embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition for the treatment or prevention of muscle atrophy associated with hip or knee replacement, hip fracture, spinal cord injury, or stroke comprising a compound as defined above~~of the invention~~ in combination with one or more pharmaceutically acceptable carriers, diluents or excipients. In yet a further embodiment, the pharmaceutical composition further comprises one or more other therapeutic agents. In another embodiment, the pharmaceutical composition has minimal risk of lowering HDL.

In a third aspect, there is provided ~~Further, the present invention provides~~ a compound ~~of the invention~~as defined above, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for treating or preventing muscle atrophy.

In a fourth aspect, there is provided~~Even further, the present invention provides~~ a compound ~~of the~~

~~Invention~~as defined above, or a pharmaceutically acceptable salt thereof, for use in treating muscle atrophy. In a further embodiment, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for treating or preventing muscle atrophy associated with hip or knee replacement, hip fracture, spinal cord injury, or stroke. Even further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in treating or preventing muscle atrophy associated with hip or knee replacement, hip fracture, spinal cord injury, or stroke. Furthermore, the present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing muscle atrophy. In a further embodiment, the present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing muscle atrophy associated with hip or knee replacement, hip fracture, spinal cord injury, or stroke.

The present ~~invention~~disclosure also provides a method of treating or preventing hypogonadism or cachexia by administering an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure further provides a method for the treatment or prevention of hypogonadism or cachexia in a patient comprising administering to a patient in need of such treatment or prevention an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. Further, the present ~~invention~~disclosure provides a compound as defined above ~~of the invention~~ or a pharmaceutically acceptable salt thereof for use in therapy, in particular for treating or preventing hypogonadism. Even further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in treating or preventing hypogonadism. Also, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for treating or preventing cachexia. Even further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in treating or preventing cachexia. Furthermore, the present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing hypogonadism or

cachexia. The present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of hypogonadism or cachexia.

The present ~~invention~~disclosure also provides a method of preventing fall-related injuries in elderly fallers with muscle weakness by administering an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure further provides a method for the prevention of fall-related injuries in elderly fallers with muscle weakness by administering an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. Further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~ or a pharmaceutically acceptable salt thereof for use in therapy, in particular for preventing fall-related injuries in elderly fallers with muscle weakness. Even further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in preventing fall-related injuries in elderly fallers with muscle weakness. Furthermore, the present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for preventing fall-related injuries in elderly fallers with muscle weakness.

The present ~~invention~~disclosure also provides a method of reversing, treating, or preventing the adverse effects of androgen deprivation therapy (ADT) by administering an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure further provides a method for the reversal, treatment, or prevention of the adverse effects of ADT in a patient comprising administering to a patient in need of such treatment or prevention an effective amount of a compound as defined above~~of the present invention~~, or a pharmaceutically acceptable salt thereof. Further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~ or a pharmaceutically acceptable salt thereof for use in therapy, in particular for reversing, treating, or preventing the adverse effects of ADT. Even further, the present ~~invention~~disclosure provides a compound as defined above~~of the invention~~, or a pharmaceutically acceptable salt thereof, for use in reversing, treating, or preventing the adverse effects of ADT. Furthermore, the present ~~invention~~disclosure provides the use of a compound as defined above~~of the invention~~, or a

pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reversing, treating, or preventing the adverse effects of ADT.

The present ~~invention~~disclosure also encompasses intermediates and processes useful for the synthesis of a compound as defined above~~of the present invention~~.

A particular method in which a compound of the present ~~invention~~disclosure is believed useful is in the treatment or prevention of muscle wasting conditions or muscle atrophy. Muscle wasting may occur as a natural result of aging (e.g. sarcopenia). Alternatively, muscle atrophy may result as a secondary consequence of disuse or inactivity (e.g. following hip or knee replacement or hip fracture), trauma, immobilization (e.g. casting or splinting of limbs), as well as spinal cord injury or stroke. (See, Hafer-Macko *et al.*, *J. Rehab. Res. Develop.*; 45(2): 261-272 (2008)) Thus, the term "muscle atrophy," as used herein, is synonymous with muscle wasting and refers to a condition wherein a patient has lost muscle mass due to a health condition such as cancer, HIV, or as a result of extended period(s) of inactivity or as an adjunct treatment following surgery where significant periods of inactivity have or may have resulted in loss of muscle mass. Further as used herein, the term "muscle atrophy associated with disuse, trauma, immobilization, spinal cord injury or stroke" refers to muscle atrophy that occurs as a secondary consequence to the incidence of disuse or inactivity (e.g. following hip or knee replacement or hip fracture), trauma, immobilization (e.g. casting or splinting of limbs), spinal cord injury or stroke. Furthermore, in the context of spinal cord injury or stroke, a compound of the present ~~invention~~disclosure may be used as an adjunct to standard rehabilitation therapy (e.g. physical or occupational therapy, exercise, assisted walking, and /or strength training). Even further, a compound of the present ~~invention~~disclosure may be used for treating or preventing co-morbidities as a result of falls due to lower limb muscle atrophy as evidenced by changes in objective measurements that assess risk of falls in the elderly (See Close and Lord, *BMJ* 2011; 343:d5153).

Another particular method in which a compound of the present ~~invention~~disclosure is believed useful is in the reversal, treatment, or prevention of the adverse effects of hormone therapy for prostate cancer, also called androgen deprivation therapy (ADT) or androgen suppression therapy.

11. A pharmaceutical composition according to Claim 9 which is formulated as a topical gel.

12. A pharmaceutical composition according to Claim 9 which is formulated as a topical cream.

13. A pharmaceutical composition according to Claim 9 which is formulated as a topical spray.

14. A pharmaceutical composition according to Claim 9 comprising a solvate.

15. A pharmaceutical composition according to Claim 14 which is 2-chloro-4-[[(1R,2R)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile • ethanol solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ = X Å) which comprises peaks at:

a) 7.00, 17.26, 12.30, and 23.34 +/- -0.2 in 2θ; or

b) 7.00, 8.59, 12.30, 16.76, 17.26, and 23.34 +/- -0.2 in 2θ; or

c) 7.00, 8.59, 10.13, 11.89, 12.30, 12.91, 13.95, 16.76, 17.26, 23.34 +/- -0.2 in 2θ.

~~16. A method for the treatment of muscle atrophy in a patient comprising administering to a patient in need of such treatment an effective amount of a compound of any of Claims 1 to 8, or a pharmaceutically acceptable salt thereof.~~

~~17. A method according to Claim 16 for the treatment of muscle atrophy associated with hip or knee replacement or hip fracture.~~

~~18.~~16. A compound of any of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~19.~~17. A compound of any of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in treating muscle atrophy.

~~20.~~18. The use of a compound of any of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of muscle atrophy.