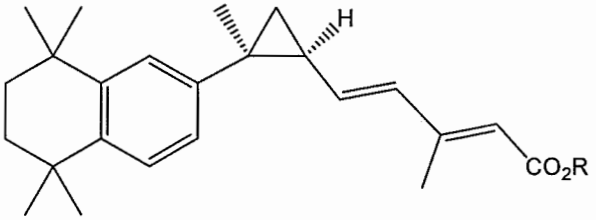
[0009a] In one aspect, there is provided the use of a RXR agonist in the manufacture of a medicament for the treatment of a muscular disorder; wherein a therapeutically effective amount of the RXR agonist is to be administered in combination with a thyroid hormone, wherein the RXR agonist has the structure of Formula II

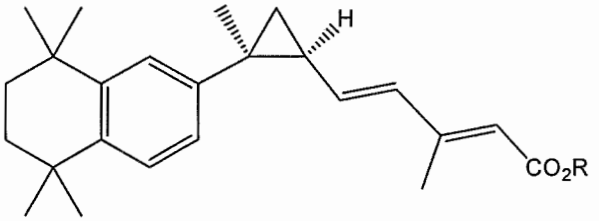


(II);

wherein R is H or lower alkyl of 1 to 6 carbon; bexarotene, or LG268 or a pharmaceutically acceptable salt thereof; and

wherein the combination to be administered shows greater efficacy in the treatment of the muscular disorder than either the medicament or the thyroid hormone alone.

[0010] In one embodiment, the RXR agonist has the structure of Formula II



(II),

wherein R is H or lower alkyl of 1 to 6 carbons. In some embodiments, the RXR agonist is a selective RXR agonist comprising 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid. In other embodiments, the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic ethyl ester. In other embodiments, the RXR agonist is bexarotene. In yet other embodiments, the RXR agonist is LG268.

[0011] In some embodiments, the thyroid hormone is thyroxine.

[0012] In some embodiments, the therapeutically effective amount of the RXR agonist is about 0.001 mg/day to about 1000 mg/day. In certain embodiments, the therapeutically effective amount of the ester of a RXR agonist is about 0.001 mg/day to about 1000 mg/day. In other embodiments, the therapeutically effective amount of the RXR agonist is about 10 mg/day to about 1000 mg/day, or 1 mg/day to 20 mg/day. In yet other embodiments, the therapeutically effective amount of thyroxine is about 12.5 µg/day to about 250 µg/day.

[0013] In some embodiments, the RXR agonist is administered by nasal administration. In other embodiments, the RXR agonist and thyroxine are both administered by nasal administration. In other embodiments, the RXR agonist is administered orally. In yet other embodiments, the thyroxine is administered orally. And in still other embodiments, the thyroxine is administered subcutaneously.

[0014] In certain embodiments, the RXR agonist and the thyroxine are both administered substantially simultaneously. In other embodiments, the RXR agonist and thyroxine are administered on different schedules.

[0015] In some embodiments, the method treats a muscle wasting disorder selected from the group consisting of acid maltase deficiency, atony, atrophy, ataxia, Becker Muscular Dystrophy (BMD), cardiac muscle ischemia, cardiac muscle infarction, a cardiomyopathy, carnitine deficiency, carnitine palmitoyltransferase deficiency, Central Core Disease (CCD), centronuclear (myotubular) myopathy, cerebral palsy, compartment syndromes, channelopathies, Congenital Muscular Dystrophy (CMD), corticosteroid myopathy, cramps, dermatomyositis, distal muscular dystrophy, Duchenne Muscular Dystrophy (DMD), dystrophinopathies, Emery-Dreifuss Muscular Dystrophy (EDMD),

Facioscapulohumeral Muscular Dystrophy (FSHD), fibromyalgia, fibrositis, Limb Girdle Muscular Dystrophy (LGMD), McArdle syndrome, muscular dystrophy, muscle fatigue, myasthenia gravis, myofascial pain syndrome, myopathy, myotonia, Myotonic Muscular Dystrophy type 1, Myotonic Muscular Dystrophy type 2, Nemaline myopathy, Oculopharyngeal Muscular Dystrophy (OCM), myoglobinuria, paramyotonia congenita (Eulenberg's disease), polymyositis, rhabdomyolysis, sarcoglycanopathies, or spasms.

[0016] In some embodiments, the myopathy is dermatomyositis, inclusion body myositis, or polymyositis.

[0017] In certain embodiments, the muscular disorder is due to cancers, HIV/AIDS, COPD, chronic steroid use, fibromyalgia, or skeletal muscle myopathies.

[0018] In other embodiments, the combination of rexinoids and thyroid hormones are beneficial by effecting heart muscle protection or regeneration either *in vivo*, or *in vitro* for subsequent implantation of myocytes into damaged cardiac muscle.

[0019] Also provided herein is a method of treating a muscular disorder, the method comprising of administering to an individual in need thereof a therapeutically effective amount of 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid, and thyroxine; and wherein administration of the combination reduces the severity of the muscular disorder in the individual by slowing or stopping progression, or inducing or hastening repair or regeneration of the affected muscle or muscles more effectively than either the RXR agonist or thyroxine alone.

[0019a] In yet another aspect, there is provided a use of 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid in the manufacture of a medicament for reducing the severity of the muscular disorder in an individual in need thereof, wherein the medicament is to be administered in combination with thyroxine; wherein the combined administration reduces the severity of the muscular disorder in the individual by slowing or stopping progression, and/or inducing or hastening repair or regeneration of the affected muscle or muscles; and wherein the combination of the medicament and the thyroid hormone to be administered shows greater efficacy in the treatment of the muscular disorder in the individual than either the RXR agonist or thyroid hormone alone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 shows RXR agonist activation of transcription from RXRα, RXRβ, RXRγ, RARα, RARβ, and RARγ using transactivation assays.

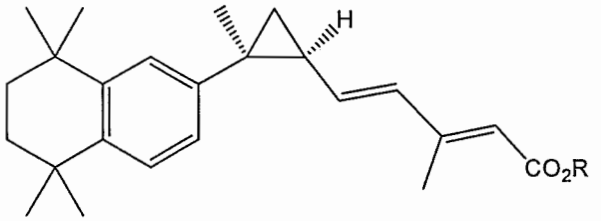
[0021] FIGS. 2A-D shows that IRX4204 selectively activates RXR-Nurr1 heterodimers. Transactivation assay of IRX4204 (194204, Formula III) for farnesoid X receptor FXR (FIG. 2A); for liver X receptors LXRα and LXRβ (FIG. 2B); for peroxisome proliferator-activated receptor PPARγ (FIG. 2C); and for Nurr1 receptor in the presence or absence of RXR (FIG. 2D).

[0022] FIG. 3 shows the percentage of green fluorescent protein (EGFP) positive oligodendrocytes after culture of oligodendrocyte precursor cells derived from embryonic mouse brains with IRX4204 and thyroid hormone.

[0023] FIG. 4 depicts changes in paw placement behavior in a rat 6-OHDA induced Parkinson Disease upon treatment with compounds and combinations described herein (*$p<0.05$ vs. vehicle using one way ANOVA followed by Dunnett test).

CLAIMS

1. Use of a RXR agonist in the manufacture of a medicament for the treatment of a muscular disorder; wherein a therapeutically effective amount of the RXR agonist is to be administered in combination with a thyroid hormone, wherein the RXR agonist has the structure of Formula II



(II);

wherein R is H or lower alkyl of 1 to 6 carbon; bexarotene, or LG268 or a pharmaceutically acceptable salt thereof; and

wherein the combination to be administered shows greater efficacy in the treatment of the muscular disorder than either the medicament or the thyroid hormone alone.

2. The use according to Claim 1, wherein is the RXR agonist is a selective RXR agonist comprising 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid.

3. The use according to Claim 1, wherein the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic ethyl ester.

4. The use according to Claim 1, wherein the RXR agonist is bexarotene.

5. The use according to Claim 1, wherein the RXR agonist is LG268.

6. The use according to Claim 1, wherein the thyroid hormone is thyroxine.

7. The use according to Claim 1, wherein the therapeutically effective amount of an ester of the RXR agonist having the structure of Formula II is about 0.001 mg/day to about 1000 mg/day.

8. The use according to Claim 1, wherein the therapeutically effective amount of the RXR agonist is about 0.001 mg/day to about 1000 mg/day.

9. The use according to Claim 1, wherein the therapeutically effective amount of the RXR agonist is about 1 mg/day to about 100 mg/day.

10. The use according to Claim 6, wherein the dose of the thyroxine is about 12.5 µg/day to about 250 µg/day.

11. The use according to Claim 1, wherein the RXR agonist is to be administered by nasal administration.

12. The use according to Claim 1, wherein the RXR agonist and the thyroid hormone are both to be administered by nasal administration.

13. The use according to Claim 1, wherein the RXR agonist is to be administered orally.

14. The use according to Claim 1, wherein the RXR agonist and the thyroid hormone are both to be administered substantially simultaneously.

15. The use according to Claim 1, wherein the RXR agonist and the thyroid hormone are to be administered on different schedules.

16. The use according to Claim 1, wherein the thyroid hormone is to be administered orally.

17. The use according to Claim 1, wherein the thyroid hormone is to be administered subcutaneously.

18. The use according to Claim 1, wherein the muscular disorder is selected from the group consisting of acid maltase deficiency, atony, atrophy, ataxia, Becker muscular dystrophy (BMD), cardiac muscle ischemia, cardiac muscle infarction, a cardiomyopathy, carnitine deficiency, carnitine palmitoyltransferase deficiency, central core disease (CCD), centronuclear (myotubular) myopathy, cerebral palsy, compartment syndromes, channelopathies, congenital muscular dystrophy (CMD), corticosteroid myopathy, cramps, dermatomyositis, Duchenne muscular dystrophy (DMD), dystrophinopathies, Emery-Dreifuss muscular dystrophy (EDMD), facioscapulohumeral muscular dystrophy (FSHD), fibrositis, limb girdle muscular dystrophy (LGMD), McArdle syndrome, muscular dystrophy, muscle fatigue, myasthenia gravis, myofascial pain syndrome, myopathy, myotonia, myotonic muscular dystrophy type 1, myotonic muscular dystrophy type 2, Nemaline myopathy, oculopharyngeal muscular dystrophy, fibromyalgia, polymyositis, rhabdomyolysis, and spasms.

19. The use according to Claim 18, wherein the myopathy is dermatomyositis, inclusion body myositis, or polymyositis.

20. The use according to Claim 18, wherein the muscular disorder is due to cancer, HIV/AIDS, COPD, or chronic steroid use.

21. The use according to claim 18, wherein the combination of retinoid agonist and the thyroid hormone is beneficial by effecting heart muscle protection or regeneration *in vivo*.

22. The use according to claim 18, wherein the combination of the RXR agonist and the thyroid hormone are beneficial for treating mycocytes *in vitro* for subsequent implantation of myocytes in a subject to regenerate heart muscle.

23. Use of 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid in the manufacture of a medicament for reducing the severity of the muscular disorder in an individual in need thereof, wherein the medicament is to be administered in combination with thyroxine; wherein the combined administration reduces the severity of the muscular disorder in the individual by slowing or stopping progression, and/or inducing or hastening repair or regeneration of the affected muscle or muscles; and wherein the combined administration shows greater efficacy in the treatment of the muscular disorder in the individual than either the RXR agonist or thyroid hormone alone.