

greater force but fatigue faster than slow skeletal muscle fibers and are functionally useful for acute, large scale movements such as rising from a chair or correcting falls. Healthy diaphragm contains approximately equal amounts of fast and slow skeletal muscle fibers, but the proportion can change under diseased conditions.

Summary of invention

[0006] In one aspect, there is provided a use of a skeletal muscle troponin activator in the manufacture of a medicament for improving diaphragm function in a patient in need thereof.

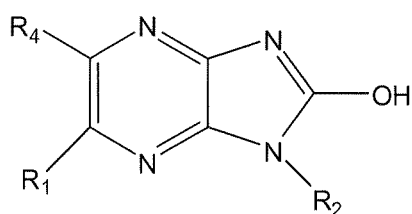
[0006a] In another aspect, there is provided a use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm of a patient in need thereof.

[0006b] In yet another aspect, there is provided a use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, force, sensitivity to calcium, or time to fatigue of a diaphragm skeletal muscle fiber.

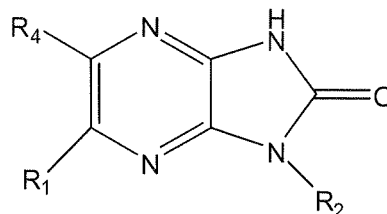
[0006c] ~~Provided~~ Also provided are compositions and methods for improving diaphragm function. In some ~~embodiments~~ examples, the methods comprise administering to a patient or contacting a diaphragm skeletal muscle fiber with an effective amount of a skeletal muscle troponin activator. Likewise, compositions and methods are also provided for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm.

[0007] In some example ~~embodiments~~, the patient receiving such administration suffers from diaphragmatic atrophy. In some example ~~embodiments~~, the patient suffers from a disease or condition selected from ventilator-induced diaphragmatic weakness or atrophy, steroid-induced diaphragmatic atrophy, hemidiaphragm paralysis, fetal hydrops, pleural effusion, botulinum poisoning, organophosphate poisoning, Guillain-Barre syndrome, phrenic nerve dysfunction, asthma, heart failure, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and muscular dystrophy. In some example ~~embodiments~~, the patient is in use of mechanical ventilation. In some example ~~embodiments~~, the patient undertakes an intense physical activity or is in an environment with a reduced partial pressure of oxygen in the air.

[0008] In some ~~embodiments~~ examples, the skeletal muscle troponin activator is a chemical entity selected from compounds of Formula A and compounds of Formula B:



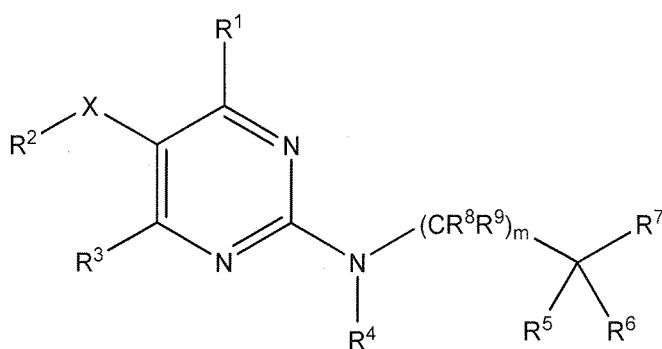
Formula A



Formula B

and pharmaceutically acceptable salts thereof, wherein R₁, R₂ and R₄ are as defined herein.

[0009] In some ~~embodiments~~ examples, the skeletal muscle troponin activator is a chemical entity selected from compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , X and m are as defined herein.

[0010] Other aspects and ~~embodiments~~ examples will be apparent to those skilled in the art from the following detailed description.

Brief Description of the Figures

[0011] **FIG. 1** shows concentration-response curves for Compound A in skinned rabbit psoas fiber and skinned rat diaphragm fiber preparations at a constant calcium concentration.

[0012] **FIG. 2** shows the force produced by skinned rat diaphragm fibers at various calcium concentrations when treated with Compound B at different concentrations.

[0013] **FIG. 3** shows the force produced by skinned rat diaphragm fibers at various calcium concentrations when treated with Compound C at different concentrations.

[0014] **FIG. 4A** shows mean diaphragm cross sectional area from SHAM and LAD rats. Mean diaphragm cross sectional area was significantly lower in HF diaphragm muscle.

[0015] **FIG. 4B** shows mean diaphragm type I myofiber area cross sectional area from SHAM and LAD rats.

[0016] **FIG. 4C** shows mean diaphragm type IIa myofiber area cross sectional area from SHAM and LAD rats. Significant atrophy can be seen in type IIa fibers in HF diaphragms.

[0017] **FIG. 4D** shows mean diaphragm type IIb/x myofiber area cross sectional area from SHAM and LAD rats. Significant atrophy can be seen in type IIb/x fibers in HF diaphragms.

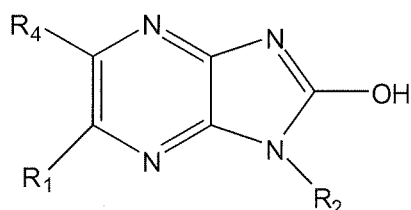
[0018] **FIG. 5** shows the force production in SHAM and HF rat diaphragm muscle measured by *ex-vivo* electrical field stimulation. HF diaphragm muscle produced significantly lower force compared to SHAM diaphragms.

CLAIMS:

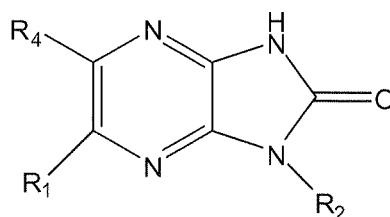
1. ~~A method for improving diaphragm function in a patient in need thereof, comprising administering to the patient an effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving diaphragm function in a patient in need thereof.
2. ~~A method for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm of a patient in need thereof, comprising administering to the patient an effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm of a patient in need thereof.
3. ~~The method-use~~ of claim 1 or 2, wherein the patient suffers from diaphragmatic atrophy.
4. ~~The method-use~~ of claim 1 or 2, wherein the patient suffers from a disease or condition selected from ventilator-induced diaphragmatic weakness or atrophy, steroid-induced diaphragmatic atrophy, hemidiaphragm paralysis, fetal hydrops, pleural effusion, botulinum poisoning, organophosphate poisoning, Guillain-Barre syndrome, phrenic nerve dysfunction, asthma, heart failure, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and muscular dystrophy.
5. ~~The method-use~~ of any one of claims 1 to 4, wherein the patient is in use of mechanical ventilation.
6. ~~The use method~~ of any one of claims 1 to 5, wherein the patient undertakes an intense physical activity or is in an environment with a reduced partial pressure of oxygen in the air.
7. ~~The use method~~ of any one of claims 1 to 6, wherein the patient has a forced vital capacity (FVC) lower than about 75% of predicted of healthy individual in similar conditions, or the patient shows evidence of increased work of breathing indicative of reduced diaphragm function.
8. ~~A method for increasing the function, activity, efficiency, force, sensitivity to calcium, or time to fatigue of a diaphragm skeletal muscle fiber, comprising contacting the fiber with an effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, force, sensitivity to calcium, or time to fatigue of a diaphragm skeletal muscle fiber.

9. The ~~method~~use of claim 2 or 8, wherein the skeletal muscle is fast skeletal muscle.

10. The ~~use method~~ of any one of claims 1 to 9, wherein the skeletal muscle troponin activator is a chemical entity selected from compounds of Formula A and compounds of Formula B:



Formula A



Formula B

and pharmaceutically acceptable salts thereof, wherein:

R₁ is alkenyl or alkynyl;

R₄ is hydrogen; and

R₂ is selected from 3-pentyl, 4-heptyl, 4-methyl-1-morpholinopentan-2-yl isobutyl, cyclohexyl, cyclopropyl, sec-butyl, tert-butyl, isopropyl, 1-hydroxybutan-2-yl, tetrahydro-2H-pyran-4-yl, 1-methoxybutan-2-yl, 1-aminobutan-2-yl, and 1-morpholinobutan-2-yl;

provided that R₁ is not hex-1-enyl.

11. The ~~use method~~ of claim 9, wherein R₁ is selected from butenyl, propenyl, vinyl, and ethynyl.

12. The ~~use method~~ of claim 11, wherein R₁ is selected from isobuten-1-yl, (Z)-propen-1-yl, (E)-propen-1-yl, propen-2-yl, vinyl, and ethynyl.

13. The ~~use method~~ of claim 11, wherein R₁ is ethynyl.

14. The ~~use method~~ of any one of claims 10 to 13, wherein R₂ is selected from 3-pentyl, 4-heptyl, 4-methyl-1-morpholinopentan-2-yl, isobutyl, sec-butyl, tert-butyl, isopropyl, 1-hydroxybutan-2-yl, tetrahydro-2H-pyran-4-yl, 1-methoxybutan-2-yl, 1-aminobutan-2-yl, and 1-morpholinobutan-2-yl.

15. The use method of claim 14, wherein R₂ is selected from 3-pentyl, 4-heptyl, isobutyl, sec-butyl, tert-butyl, isopropyl, and 1-hydroxybutan-2-yl.

16. The use method of claim 15, wherein R₂ is selected from 3-pentyl, 4-heptyl, isobutyl, sec-butyl, tert-butyl, and isopropyl.

17. The use method of claim 10, wherein the compound of Formula A is selected from:

1-(ethylpropyl)-6-ethynylimidazo[4,5-b]pyrazin-2-ol;
1-[(1R)-1-(morpholin-4-ylmethyl)propyl]-6-ethynylimidazo[4,5-b]pyrazin-2-ol;
(E)-1-(pentan-3-yl)-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(E)-1-(pentan-3-yl)-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(E)-1-cyclohexyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(E)-1-cyclopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(E)-1-isopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(E)-6-(prop-1-enyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(Z)-1-(pentan-3-yl)-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(Z)-1-cyclohexyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(Z)-1-cyclopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(Z)-1-isopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
(Z)-6-(prop-1-enyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2-ol;
1-(pentan-3-yl)-6-(prop-1-ynyl)-1H-imidazo[4,5-b]pyrazin-2-ol;
6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol;
1-(ethylpropyl)-6-vinylimidazo[4,5-b]pyrazin-2-ol; and
1-(ethylpropyl)-6-(1-methylvinyl)imidazo[4,5-b]pyrazin-2-ol;

or a pharmaceutically acceptable salt thereof.

18. The use method of claim 10, wherein the compound of Formula B is selected from:

6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-6-ethynyl-1-(1-morpholinobutan-2-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(E)-1-(pentan-3-yl)-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(E)-1-cyclohexyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

(E)-1-cyclopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (E)-1-isopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (E)-6-(prop-1-enyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (Z)-1-(pentan-3-yl)-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (Z)-1-cyclohexyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (Z)-1-cyclopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (Z)-1-isopropyl-6-(prop-1-enyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 (Z)-6-(prop-1-enyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 1-(pentan-3-yl)-6-(prop-1-ynyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
 1-(pentan-3-yl)-6-vinyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one; and
 1-(pentan-3-yl)-6-(prop-1-en-2-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

or a pharmaceutically acceptable salt thereof.

19. The use method of claim 10, wherein the chemical entity is selected from 1-(ethylpropyl)-6-ethynylimidazo[4,5-b]pyrazin-2-ol, 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol, and 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one, or a pharmaceutically acceptable salt thereof.

20. The use method of claim 10, wherein the chemical entity is 6-bromo-1-(ethylpropyl)imidazo[4,5-b]pyrazin-2-ol or a pharmaceutically acceptable salt thereof.

21. The use method of claim 10, wherein the chemical entity is 1-(ethylpropyl)-6-ethynylimidazo[4,5-b]pyrazin-2-ol or a pharmaceutically acceptable salt thereof.

22. The use method of any one of claims 1 to 9, wherein the skeletal muscle troponin activator is a chemical entity selected from compounds of Formula I:

R^h , at each occurrence, is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, C_{7-11} aralkyl and 5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, C_{7-11} aralkyl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^k substituents;

R^i and R^j , at each occurrence, are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, C_{7-11} aralkyl, 5-10 membered heteroaryl, $C(O)R^g$, and $C(O)OR^g$, wherein each of the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, C_{7-11} aralkyl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, OH, C_{1-6} alkoxy, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^k , at each occurrence, is independently selected from halogen, CN, OH, C_{1-6} alkoxy, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHC(O)C_{1-6} \text{ alkyl}$, $NHC(O)C_{7-11} \text{ aralkyl}$, $NHC(O)OC_{1-6} \text{ alkyl}$, $NHC(O)OC_{7-11} \text{ aralkyl}$, $OC(O)C_{1-6} \text{ alkyl}$, $OC(O)C_{7-11} \text{ aralkyl}$, $OC(O)OC_{1-6} \text{ alkyl}$, $OC(O)OC_{7-11} \text{ aralkyl}$, $C(O)C_{1-6} \text{ alkyl}$, $C(O)C_{7-11} \text{ aralkyl}$, $C(O)OC_{1-6} \text{ alkyl}$, $C(O)OC_{7-11} \text{ aralkyl}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{7-11} aralkyl substituent is optionally substituted with 1, 2 or 3 substituents selected from OH, C_{1-6} alkoxy, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHC(O)C_{1-6} \text{ alkyl}$, $NHC(O)C_{7-11} \text{ aralkyl}$, $NHC(O)OC_{1-6} \text{ alkyl}$, and $NHC(O)OC_{7-11} \text{ aralkyl}$;

or two R^k substituents bound to a single carbon atom, together with the carbon atom to which they are both bound, form a carbonyl group;

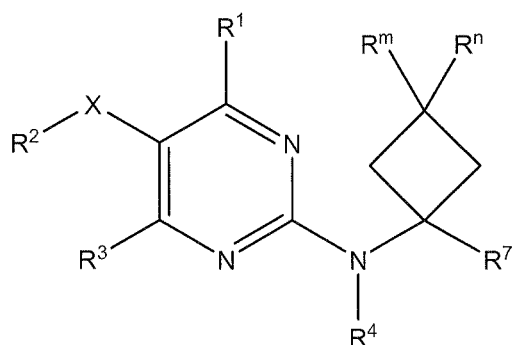
m is 0, 1 or 2;

n , at each occurrence, independently is 0, 1 or 2;

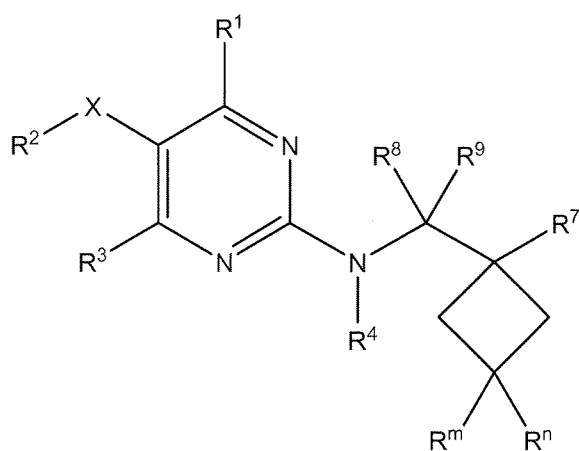
p is 0, 1 or 2; and

q is 0, 1 or 2.

23. The ~~use method~~ of claim 22, wherein the chemical entity is of Formula V(a) or V(b), or a pharmaceutically acceptable salt thereof:



Formula V(a)



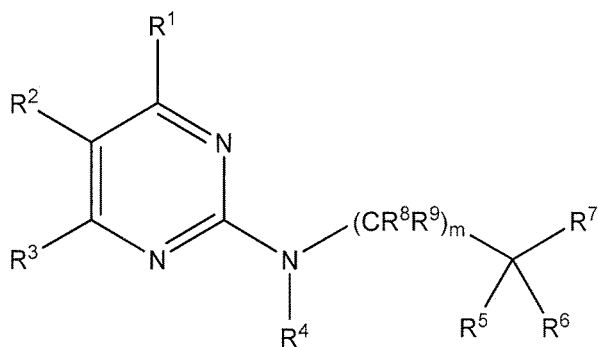
or

Formula V(b)

wherein R^m and Rⁿ are each independently selected from hydrogen, halogen and C₁₋₆ alkyl.

24. The use method of claim 22 or 23, wherein X is a bond.

25. The use method of claim 24, wherein the chemical entity is of Formula XII(a), or a pharmaceutically acceptable salt thereof:



Formula XII(a).

26. The use method of claim 22, wherein the chemical entity is
1-(2-(((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methylamino)pyrimidin-5-yl)-1H-pyrrole-3
-carboxamide.

27. The use method of claim 22, wherein the chemical entity is
3-(2-(((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methylamino)pyrimidin-5-yl) benzamide.