associated with various somatosensory signals, emotional state, discomfort, pain, thermal stress and thirst (Noakes et al. *Br J Sports Med.* August; 38(4): 511–514, 2004, J.W. Williamson, *Exp Physiol* 95: 1043–1048, 2010). This integrated mechanism works to preserve the integrity of the system by initiating muscle fatigue through inhibition of muscle recruitment, and as a result, maximal voluntary strength can be below the true maximal muscle force. Alteration in perceived effort, as is possible in the presence of a skeletal troponin activator, can mitigate fatigue.

[0005] The means to decrease fatigue in certain situations has therapeutic potential, especially in a number of disease settings, including heart failure. Muscle function can become compromised in disease by many mechanisms. Accordingly, there is a need for the development of new compounds that modulate skeletal muscle contractility and of new methods for improving resistance to skeletal muscle fatigue.

Summary

[0006] Provided are compounds, compositions and methods for improving resistance to skeletal muscle fatigue.

In one aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to skeletal muscle fatigue in a subject suffering from heart failure. In some examples, the method comprises administering to a subject an effective amount of a skeletal muscle troponin activator. In some examples, the skeletal muscle fatigue is selected from central fatigue, peripheral fatigue, and a combination thereof. In some examples, the skeletal muscle troponin activator is a fast skeletal muscle troponin activator. In some examples, the subject is suffering from a condition selected from peripheral artery disease, claudication, and muscle ischemia.

[0007] Also provided are methods for improving physical endurance or reducing exercise intolerance in a subject, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0008] In another ~~aspect~~example, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to a fatigue in a skeletal muscle. Also provided are methods of improving resistance to fatigue in a skeletal muscle, comprising contacting the skeletal muscle with a skeletal muscle troponin activator, wherein the skeletal muscle troponin activator increases submaximal tension in the skeletal muscle.

[0009] Also provided are methods of improving resistance to fatigue in a skeletal muscle, comprising contacting the skeletal muscle with a skeletal muscle troponin activator, wherein the

subject an effective amount of a skeletal muscle troponin activator. In some examples, the skeletal muscle troponin activator is a fast skeletal muscle troponin activator. Similarly, the compounds, compositions and methods described and/or disclosed herein may be used to improve exercise tolerance.

[0011] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for treating exercise intolerance in a patient suffering from heart failure.
Also provided are methods for treating exercise intolerance associated with heart failure in a subject, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0012] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving physical endurance performance of a patient suffering from heart failure.
Also provided are methods for improving physical endurance of a patient suffering from heart failure, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0013] In another aspect, there is provided 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 of a patient suffering from heart failure.Also provided are methods for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle of a patient suffering from heart failure, comprising administering to the patient an effective amount of a skeletal muscle troponin activator.

[0014] In another ~~aspect~~example, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving skeletal muscle function of a patient suffering from heart failure. Also provided are methods for improving skeletal muscle function of a patient suffering from heart failure, comprising administering to the patient an effective amount of a skeletal muscle troponin activator.

[0015] Also provided are methods for improving resistance to skeletal muscle fatigue in a subject in need thereof, comprising administering to the subject an effective amount of a skeletal muscle troponin activator, wherein the improvement in resistance to fatigue in the subject is determined by a bilateral heel-raise test. In some examples, the bilateral heel-raise test comprises: instructing the subject to perform heel raises at regular intervals; and measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal

Claims:

1. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to skeletal muscle fatigue in a subject.

2. The use of claim 1, wherein the subject is suffering from a condition selected from peripheral artery disease, claudication, and muscle ischemia.

3. The use of claim 1, wherein the subject is suffering from heart failure.

4. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to fatigue in a skeletal muscle.

5. The use of any one of claims 1 to 4, wherein the skeletal muscle troponin activator increases submaximal tension in the skeletal muscle.

6. The use of any one of claims 1 to 5, wherein the skeletal muscle troponin activator reduces the intracellular calcium required by the skeletal muscle to generate force.

7. The use of any one of claims 1 to 3, wherein the improvement in resistance to fatigue in the subject is determined by a bilateral heel-raise test comprising:

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to fatigue in the subject.

8. The use of claim 7, wherein the parameter is time to claudication onset.

9. The use of claim 7, wherein the parameter is number of heel raises to claudication onset.

10. The use of claim 7, wherein the parameter is work to claudication onset.

11. The use of claim 7, wherein the parameter is time to maximal claudication fatigue.

12. The use of claim 7, wherein the parameter is number of heel raises to maximal claudication fatigue.

13. The use of claim 7, wherein the parameter is work to maximal claudication fatigue.

14. Use of a skeletal muscle troponin activator in the manufacture of a medicament for treating exercise intolerance in a patient suffering from heart failure.

15. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving physical endurance performance of a patient suffering from heart failure.

16. 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 of a patient suffering from heart failure.

17. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving skeletal muscle function of a patient suffering from heart failure.

18. The use of any one of claims 14 to 17, wherein the medicament further comprises a second therapy.

19. The use of claim 18, wherein the second therapy is selected from an antiplatelet drug, a diuretic, a calcium channel blocker, a beta blocker, an ACE inhibitor, a statin, an angiotensin II receptor antagonist, and an aldosterone antagonist.

20. The use of claim 19, wherein the second therapy is selected from digoxin, aspirin, ticlopidine, clopidogrel, metoprolol, carvedilol, eplerenone, and spironolactone.

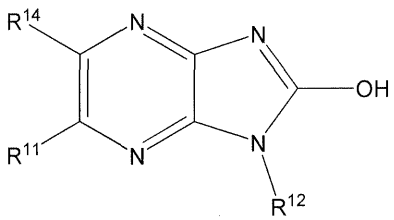
21. The use of claim 18, wherein the second therapy is selected from angioplasty, stenting, and surgery.

22. The use of any one of claims 18 to 21 wherein the skeletal muscle troponin activator and the second therapy are to be administered simultaneously to the subject.

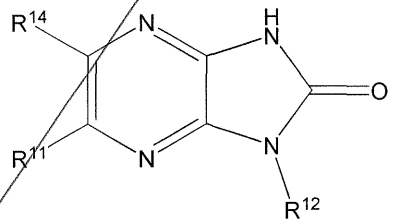
23. The use of any one of claims 18 to 21 wherein the skeletal muscle troponin activator and the second therapy are to be administered sequentially to the subject.

24. The use of any one of claims 1 to 23, wherein the skeletal muscle troponin activator is a fast skeletal muscle troponin activator.

25. The use of any one of claims 1 to 24, wherein the skeletal muscle troponin activator is selected from compounds of Formula A and Formula B:



Formula A



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is alkenyl or alkynyl;

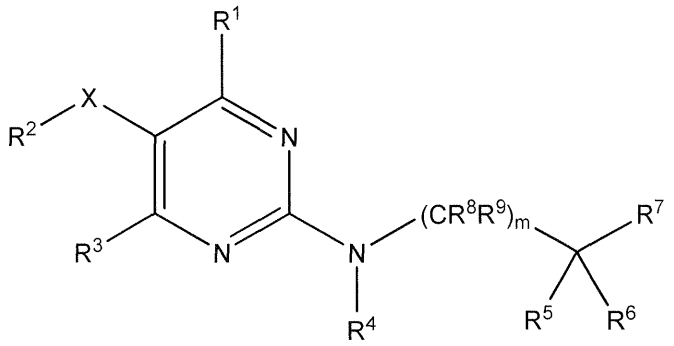
R^{14} is hydrogen; and

R^{12} is selected from 3-pentyl, 4-heptyl, 4-methyl-1-morpholinopentan-2-yl isobutyl, cyclohexyl, cyclopropyl, sec-butyl, tert-butyl, isopropyl, 1-hydroxybutan-2yl, tetrahydro-2H-pyran-4-yl, 1-methoxybutan-2-yl, 1-aminobutan-2-yl, and 1-morpholinobutan-2-yl;

provided that R^{11} is not hex-1-enyl.

26. The use of claim 25, wherein the skeletal muscle troponin activator is 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol, or a pharmaceutically acceptable salt thereof.

27. The use of any one of claims 1 to 24, wherein the skeletal muscle troponin activator is selected from compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^2 is selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, 5-10 membered heteroaryl and NR^bR^c, wherein each of the C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R^3 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$ and SO_2R^a;

R^5 and R^6 are each independently selected from hydrogen, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

or alternatively, R^5 and R^6 together with the carbon atom to which they are bound form a group selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl

and 3-8 membered heterocycloalkenyl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^7 is selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl and 5-10 membered heteroaryl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, $OC(O)NR^bR^c$, NR^bR^c, $NR^dC(O)R^a$, $NR^dC(O)OR^a$, $NR^dC(O)NR^bR^c$, $NR^dC(O)C(O)NR^bR^c$, $NR^dC(S)R^a$, $NR^dC(S)OR^a$, $NR^dC(S)NR^bR^c$, $NR^dC(NR^e)NR^bR^c$, $NR^dS(O)R^a$, $NR^dSO_2R^a$, $NR^dSO_2NR^bR^c$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(S)R^a$, $C(S)OR^a$, $C(S)NR^bR^c$, $C(NR^e)NR^bR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, 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^f substituents;

R^8 and R^9, at each occurrence, are each independently selected from hydrogen, halogen and C_{1-6} alkyl;

X is selected from a bond, $-(CH_2)_p-$, $-(CH_2)_pC(O)(CH_2)_q-$, $-(CH_2)_pO(CH_2)_q-$, $-(CH_2)_pS(CH_2)_q-$, $-(CH_2)_pNR^d(CH_2)_q-$, $-(CH_2)_pC(O)O(CH_2)_q-$, $-(CH_2)_pOC(O)(CH_2)_q-$, $-(CH_2)_pNR^dC(O)(CH_2)_q-$, $-(CH_2)_pC(O)NR^d(CH_2)_q-$, $-(CH_2)_pNR^dC(O)NR^d(CH_2)_q-$, $-(CH_2)_pNR^dSO_2(CH_2)_q-$, and $-(CH_2)_pSO_2NR^d(CH_2)_q-$;

or alternatively, X, R^2 and R^3, together with the carbon atoms to which they are bound, form a 5-6 membered ring optionally containing one or more heteroatoms selected from oxygen nitrogen and sulfur, and optionally containing one or more double bonds, and optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R^a, 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^f substituents;

R^b and R^c, 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, $C(O)R^g$, $C(O)OR^g$, $C(O)NR^iR^j$ and SO_2R^g, 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^f substituents;

R^d, at each occurrence, is independently selected from hydrogen and C_{1-6} alkyl;

R^e, at each occurrence, is independently selected from hydrogen, CN, OH, C_{1-6} alkoxy, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^f, at each occurrence, is independently selected from halogen, CN, OR^h, $OC(O)R^h$, $OC(O)OR^h$, $OC(O)NR^iR^j$, NR^iR^j, $NR^dC(O)R^h$, $NR^dC(O)OR^h$, $NR^dC(O)NR^iR^j$, $NR^dC(O)C(O)NR^iR^j$, $NR^dC(S)R^h$, $NR^dC(S)OR^h$, $NR^dC(S)NR^iR^j$, $NR^dC(NR^e)NR^iR^j$, $NR^dS(O)R^h$, $NR^dSO_2R^h$, $NR^dSO_2NR^iR^j$, $C(O)R^h$, $C(O)OR^h$, $C(O)NR^iR^j$, $C(S)R^h$, $C(S)OR^h$, $C(S)NR^iR^j$, $C(NR^e)NR^iR^j$, SR^h, $S(O)R^h$, SO_2R^h, $SO_2NR^iR^j$, 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;

or two R^f substituents bound to a single carbon atom, together with the carbon atom to which they are both bound, form a group selected from carbonyl, C_{3-8} cycloalkyl and 3-8 membered heterocycloalkyl;

R^g, at each occurrence, is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, naphthyl, and C_{7-11} aralkyl, each 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^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, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, $NHC(O)OC_{7-11}$ aralkyl, $OC(O)C_{1-6}$ alkyl, $OC(O)C_{7-11}$ aralkyl, $OC(O)OC_{1-6}$ alkyl, $OC(O)OC_{7-11}$ aralkyl, $C(O)C_{1-6}$ alkyl, $C(O)C_{7-11}$ aralkyl, $C(O)OC_{1-6}$ alkyl, $C(O)OC_{7-11}$ 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, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, and $NHC(O)OC_{7-11}$ 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.

28. Use of a skeletal muscle troponin activator in the manufacture of a medicament for determining the efficacy of a skeletal muscle troponin activator in a subject in improving resistance to skeletal muscle fatigue, wherein said medicament is to be administered into the subject and wherein the improvement in resistance is determined by:

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to skeletal muscle fatigue in the subject.

29. The use of claim 28, wherein the parameter is time to claudication onset.

30. The use of claim 28, wherein the parameter is number of heel raises to claudication onset.

31. The use of claim 28, wherein the parameter is work to claudication onset.

32. The use of claim 28, wherein the parameter is time to maximal claudication fatigue.

33. The use of claim 28, wherein the parameter is number of heel raises to maximal claudication fatigue.

34. The use of claim 28, wherein the parameter is work to maximal claudication fatigue.

Claims:

1. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to skeletal muscle fatigue in a subject suffering from heart failure.

2. The use of claim 1, wherein the skeletal muscle troponin activator increases submaximal tension in the skeletal muscle.

3. The use of claim 1 or 3, wherein the skeletal muscle troponin activator reduces the intracellular calcium required by the skeletal muscle to generate force.

4. The use of any one of claims 1 to 3, wherein the improvement in resistance to fatigue in the subject is determined by a bilateral heel-raise test comprising:

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to fatigue in the subject.

5. The use of claim 4, wherein the parameter is time to claudication onset.

6. The use of claim 4, wherein the parameter is number of heel raises to claudication onset.

7. The use of claim 4, wherein the parameter is work to claudication onset.

8. The use of claim 4, wherein the parameter is time to maximal claudication fatigue.

9. The use of claim 4, wherein the parameter is number of heel raises to maximal claudication fatigue.

10. The use of claim 4, wherein the parameter is work to maximal claudication fatigue.

11. Use of a skeletal muscle troponin activator in the manufacture of a medicament for treating exercise intolerance in a patient suffering from heart failure.

12. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving physical endurance performance of a patient suffering from heart failure.

13. 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 of a patient suffering from heart failure.

14. The use of any one of claims 1 to 13, wherein the medicament further comprises a second therapy.

15. The use of claim 14, wherein the second therapy is selected from an antiplatelet drug, a diuretic, a calcium channel blocker, a beta blocker, an ACE inhibitor, a statin, an angiotensin II receptor antagonist, and an aldosterone antagonist.

16. The use of claim 15, wherein the second therapy is selected from digoxin, aspirin, ticlopidine, clopidogrel, metoprolol, carvedilol, eplerenone, and spironolactone.

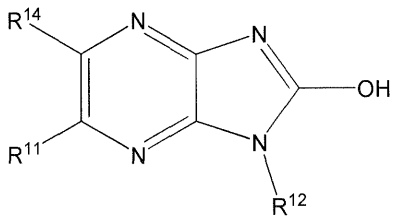
17. The use of claim 14, wherein the second therapy is selected from angioplasty, stenting, and surgery.

18. The use of any one of claims 14 to 17 wherein the skeletal muscle troponin activator and the second therapy are to be administered simultaneously to the subject.

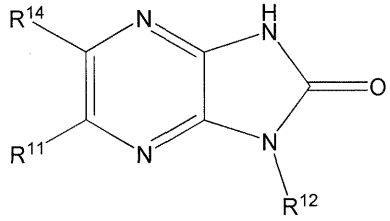
19. The use of any one of claims 14 to 17 wherein the skeletal muscle troponin activator and the second therapy are to be administered sequentially to the subject.

20. The use of any one of claims 1 to 19, wherein the skeletal muscle troponin activator is a fast skeletal muscle troponin activator.

21. The use of any one of claims 1 to 20, wherein the skeletal muscle troponin activator is selected from compounds of Formula A and Formula B:



Formula A



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is alkenyl or alkynyl;

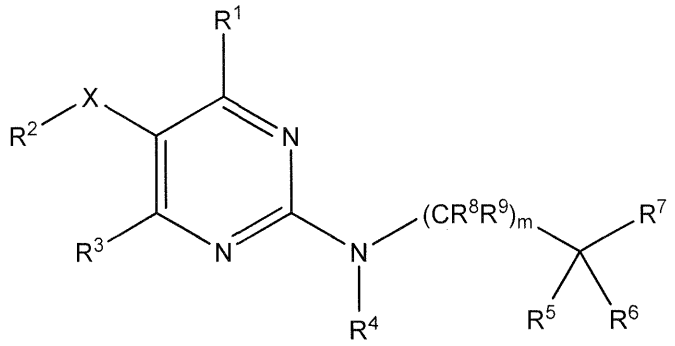
R^{14} is hydrogen; and

R^{12} is selected from 3-pentyl, 4-heptyl, 4-methyl-1-morpholinopentan-2-yl isobutyl, cyclohexyl, cyclopropyl, sec-butyl, tert-butyl, isopropyl, 1-hydroxybutan-2yl, tetrahydro-2H-pyran-4-yl, 1-methoxybutan-2-yl, 1-aminobutan-2-yl, and 1-morpholinobutan-2-yl;

provided that R^{11} is not hex-1-enyl.

22. The use of claim 21, wherein the skeletal muscle troponin activator is 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol, or a pharmaceutically acceptable salt thereof.

23. The use of any one of claims 1 to 20, wherein the skeletal muscle troponin activator is selected from compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^2 is selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, 5-10 membered heteroaryl and NR^bR^c, wherein each of the C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R^3 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$ and SO_2R^a;

R^5 and R^6 are each independently selected from hydrogen, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

or alternatively, R^5 and R^6 together with the carbon atom to which they are bound form a group selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl and 3-8 membered heterocycloalkenyl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^7 is selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl and 5-10 membered heteroaryl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, $OC(O)NR^bR^c$, NR^bR^c, $NR^dC(O)R^a$, $NR^dC(O)OR^a$, $NR^dC(O)NR^bR^c$, $NR^dC(O)C(O)NR^bR^c$, $NR^dC(S)R^a$, $NR^dC(S)OR^a$, $NR^dC(S)NR^bR^c$, $NR^dC(NR^e)NR^bR^c$, $NR^dS(O)R^a$,

$NR^dSO_2R^a$, $NR^dSO_2NR^bR^c$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(S)R^a$, $C(S)OR^a$, $C(S)NR^bR^c$, $C(NR^e)NR^bR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, 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^f substituents;

R^8 and R^9, at each occurrence, are each independently selected from hydrogen, halogen and C_{1-6} alkyl;

X is selected from a

bond, $-(CH_2)_p-$, $-(CH_2)_pC(O)(CH_2)_q-$, $-(CH_2)_pO(CH_2)_q-$, $-(CH_2)_pS(CH_2)_q-$, $-(CH_2)_pNR^d(CH_2)_q-$, $-(CH_2)_pC(O)O(CH_2)_q-$, $-(CH_2)_pOC(O)(CH_2)_q-$, $-(CH_2)_pNR^dC(O)(CH_2)_q-$, $-(CH_2)_pC(O)NR^d(CH_2)_q-$, $-(CH_2)_pNR^dC(O)NR^d(CH_2)_q-$, $-(CH_2)_pNR^dSO_2(CH_2)_q-$, and $-(CH_2)_pSO_2NR^d(CH_2)_q-$;

or alternatively, X, R^2 and R^3, together with the carbon atoms to which they are bound, form a 5-6 membered ring optionally containing one or more heteroatoms selected from oxygen nitrogen and sulfur, and optionally containing one or more double bonds, and optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R^a, 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^f substituents;

R^b and R^c, 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, $C(O)R^g$, $C(O)OR^g$, $C(O)NR^iR^j$ and SO_2R^g, 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^f substituents;

R^d, at each occurrence, is independently selected from hydrogen and C_{1-6} alkyl;

R^e, at each occurrence, is independently selected from hydrogen, CN, OH, C_{1-6} alkoxy, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^f, at each occurrence, is independently selected from halogen, CN, OR^h, $OC(O)R^h$, $OC(O)OR^h$, $OC(O)NR^iR^j$, NR^iR^j, $NR^dC(O)R^h$, $NR^dC(O)OR^h$, $NR^dC(O)NR^iR^j$, $NR^dC(O)C(O)NR^iR^j$, $NR^dC(S)R^h$, $NR^dC(S)OR^h$, $NR^dC(S)NR^iR^j$, $NR^dC(NR^e)NR^iR^j$, $NR^dS(O)R^h$, $NR^dSO_2R^h$, $NR^dSO_2NR^iR^j$, $C(O)R^h$, $C(O)OR^h$, $C(O)NR^iR^j$, $C(S)R^h$, $C(S)OR^h$, $C(S)NR^iR^j$, $C(NR^e)NR^iR^j$, SR^h, $S(O)R^h$, SO_2R^h, $SO_2NR^iR^j$, 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;

or two R^f substituents bound to a single carbon atom, together with the carbon atom to which they are both bound, form a group selected from carbonyl, C_{3-8} cycloalkyl and 3-8 membered heterocycloalkyl;

R^g, at each occurrence, is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, naphthyl, and C_{7-11} aralkyl, each 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^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, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, $NHC(O)OC_{7-11}$ aralkyl, $OC(O)C_{1-6}$ alkyl, $OC(O)C_{7-11}$ aralkyl, $OC(O)OC_{1-6}$ alkyl, $OC(O)OC_{7-11}$ aralkyl, $C(O)C_{1-6}$ alkyl, $C(O)C_{7-11}$ aralkyl, $C(O)OC_{1-6}$ alkyl, $C(O)OC_{7-11}$ 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, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, and $NHC(O)OC_{7-11}$ 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.

24. The use of claim 23, wherein m is 1.

25. The use of claim 23, wherein X is a bond.

26. The use of claim 24, wherein R^8 and R^9 are each hydrogen.

27. The use of any one of claims 23 to 26, wherein R^5 and R^6 together with the carbon atom to which they are bound form C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered

heterocycloalkyl and 3-8 membered heterocylocalkenyl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bNR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl.

28. The use of claim 27, wherein R^5 and R^6 together with the carbon atom to which they are bound form C_{3-8} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bNR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl.

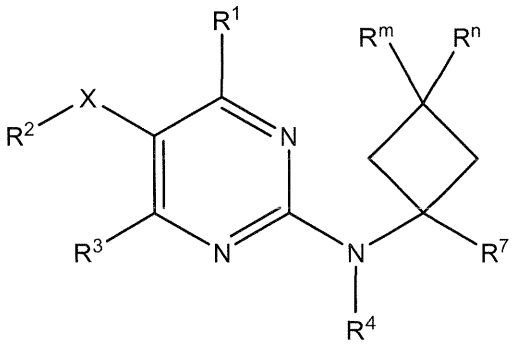
29. The use of claim 28, wherein R^5 and R^6 together with the carbon atom to which they are bound form a group selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, each optionally substituted with 1,2,3,4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bNR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl.

30. The use of claim 29, wherein R^5 and R^6 together with the carbon atom to which they are bound form cyclobutyl optionally substituted with 1,2,3,4 or 5 substituents selected from halogen, CN, oxo, OR^a, $OC(O)R^a$, $OC(O)OR^a$, NR^bNR^c, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, C_{1-6} alkyl and C_{1-6} haloalkyl.

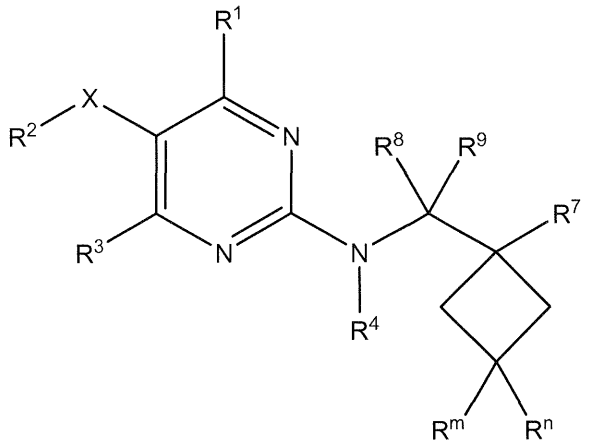
31. The use of claim 30, wherein R^5 and R^6 together with the carbon atom to which they are bound form cyclobutyl substituted with one or two halogens.

32. The use of claim 31, wherein R^5 and R^6 together with the carbon atom to which they are bound form a group selected from cyclobutyl, 3-fluorocyclobutyl and 3,3-difluorocyclobutyl.

33. The use of claim 30, wherein the compound of Formula I is a compound of Formula V(a) or V(b), or a pharmaceutically acceptable salt thereof:



Formula V(a)



Formula V(b)

wherein R^m and R^n are each independently selected from hydrogen and halogen and the substituents labeled R^1-R^4 & R^7-R^9 are identical to those in claim 23.

34. The use of claim 33, wherein X is a bond.

35. The use of claim 33, wherein one of R^m and R^n is hydrogen and the other is halogen.

36. The use of claim 33, wherein the halogen and R^7 are in a *trans* configuration with respect to one another on the cyclobutyl ring.

37. The use of claim 33, wherein the halogen and R^7 are in a *cis* configuration with respect to one another on the cyclobutyl ring.

38. The use of any one of claims 33-37, wherein one of R^m and R^n is hydrogen and the other is fluorine.

39. The use of any one of claims 23-38, wherein R^7 is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $O(CO)OR^a$, $OC(O)R^a$, $OC(O)NR^bR^c$, NR^bR^c, $NR^dC(O)R^a$, $NR^dC(O)OR^a$, $NR^dC(O)NR^bR^c$, $NR^dC(O)C(O)NR^bR^c$, $NR^dC(S)R^a$, $NR^dC(S)OR^a$, $NR^dC(S)NR^bR^c$, $NR^dC(NR^e)NR^bR^c$, $NR^dS(O)R^a$, $NR^dSO_2R^a$, $NR^dSO_2NR^bR^c$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(S)R^a$, $C(S)OR^a$, $C(S)NR^bR^c$, $C(NR^e)NR^bR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, 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^f substituents.

40. The use of claim 39, wherein R^7 is pyridyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $O(CO)OR^a$, $OC(O)R^a$, $OC(O)NR^bR^c$, NR^bR^c, $NR^dC(O)R^a$, $NR^dC(O)OR^a$, $NR^dC(O)NR^bR^c$, $NR^dC(O)C(O)NR^bR^c$, $NR^dC(S)R^a$, $NR^dC(S)OR^a$, $NR^dC(S)NR^bR^c$, $NR^dC(NR^e)NR^bR^c$, $NR^dS(O)R^a$, $NR^dSO_2R^a$, $NR^dSO_2NR^bR^c$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(S)R^a$, $C(S)OR^a$, $C(S)NR^bR^c$, $C(NR^e)NR^bR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, 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^f substituents.

41. The use of claim 40, wherein R^7 is 2-pyridyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, OR^a, $O(CO)OR^a$, $OC(O)R^a$, $OC(O)NR^bR^c$, NR^bR^c, $NR^dC(O)R^a$, $NR^dC(O)OR^a$, $NR^dC(O)NR^bR^c$, $NR^dC(O)C(O)NR^bR^c$, $NR^dC(S)R^a$, $NR^dC(S)OR^a$, $NR^dC(S)NR^bR^c$, $NR^dC(NR^e)NR^bR^c$, $NR^dS(O)R^a$, $NR^dSO_2R^a$, $NR^dSO_2NR^bR^c$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(S)R^a$, $C(S)OR^a$, $C(S)NR^bR^c$, $C(NR^e)NR^bR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^bR^c$, 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^f substituents.

42. The use of any one of claims 23-38, wherein R^2 is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl, and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl, and

$(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents.

43. The use of claim 42, wherein R^2 is selected from pyridyl, pyrimidyl, pyrazyl, pyridazyl, triazyl, furanyl, pyrrolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, triazolyl and tetrazolyl, each optionally substituted with 1, 2, 3 or 4 substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl,and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl,and $(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents.

44. The use of claim 43, wherein R^2 is selected from pyridyl, pyrimidyl, pyrazyl, pyridazyl, triazyl, furanyl, pyrrolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, triazolyl and tetrazolyl, each optionally substituted with a substituent selected from $(CH_2)_nC(O)OR^a$ and $(CH_2)_nC(O)NR^bR^c$; and optionally substituted with 1, 2 or 3 additional substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl,and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$naphthyl,and $(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents.

45. The use of claim 44, wherein R^2 is selected from furanyl, pyrrolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, triazolyl and tetrazolyl, each substituted with $(CH_2)_nC(O)NR^bR^c$.

46. The use of any one of claims 23-45, wherein R^1 is selected from hydrogen, halogen, CN, CF_3 and methyl.

47. The use of claim 46, wherein R^1 is hydrogen.

48. The use of any one of claims 23-47, wherein R^3 is selected from hydrogen, halogen, CN, CF_3 and methyl.

49. The use of claim 48, wherein R^3 is hydrogen.

50. The use of any one of claims 23-49, wherein R^4 is hydrogen.

51. The use of claim 23, wherein the skeletal muscle troponin activator of Formula I is selected from: 1-(2-((3-fluoro-1-(3-fluoropyridin-2-yl) cyclobutyl)methylamino)pyrimidin-5-yl)-1*H*-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.

52. The use of claim 24, wherein the skeletal muscle troponin activator of Formula I is selected from: 1-(2-(((trans)-3-fluoro-1-(3-fluoropyridin-2-yl) cyclobutyl)methylamino)pyrimidin-5-yl)-1*H*-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.