

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. use of a chemical entity selected from 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, in the manufacture of a medicament for improving diaphragm function in a patient suffering 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.

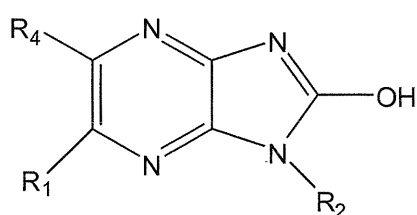
[0006a] In another aspect, there is provided a use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm of a patient in need thereof. use of a chemical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

[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. use of a chemical entity selected from 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, 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 in a patient suffering 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.

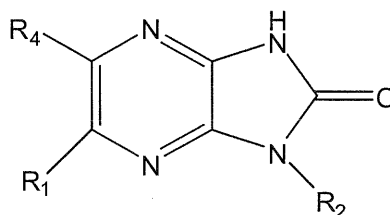
[0006c] Also provided are compositions and methods for improving diaphragm function. In some examples, the methods comprise administering to a patient or contacting a diaphragm skeletal muscle fiber with an effective amount of a skeletal muscle troponin activator. Likewise, compositions and methods are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

[0007] In some examples, the patient receiving such administration suffers from diaphragmatic atrophy. In some examples, 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 examples, the patient is in use of mechanical ventilation. In some examples, 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 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 R_1 , R_2 and R_4 are as defined herein.

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

CLAIMS:

1. Use of a chemical entity selected from 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, in the manufacture of a medicament for improving diaphragm function in a patient suffering 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.
2. Use of a chemical entity selected from 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, 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 suffering 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.
3. The use of claim 1 or 2, wherein the patient suffers from diaphragmatic atrophy.
4. The use of claim 1 or 2, wherein the patient suffers from amyotrophic lateral sclerosis (ALS).
5. The use of any one of claims 1 to 4, wherein the chemical entity selected from 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, is to be co-administered with mechanical ventilation.
6. Use of a chemical entity selected from 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, 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 in a patient suffering 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.

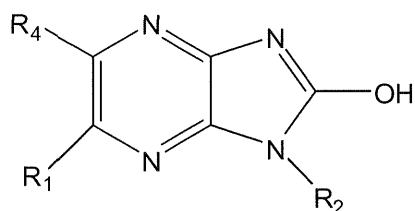
7. The use of claim 2 or 6, wherein the skeletal muscle is fast skeletal muscle.

CLAIMS:

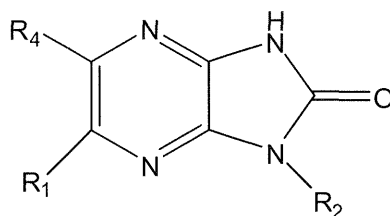
1. Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving diaphragm function in a patient in need thereof.
2. Use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle in the diaphragm of a patient in need thereof.
3. The use of claim 1 or 2, wherein the patient suffers from diaphragmatic atrophy.
4. The 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 use of any one of claims 1 to 4, wherein the patient is in use of mechanical ventilation.
6. The use 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 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. 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 use of claim 2 or 8, wherein the skeletal muscle is fast skeletal muscle.

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

12. The use 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 of claim 11, wherein R₁ is ethynyl.

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

17. The use 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 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-enyl)-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;

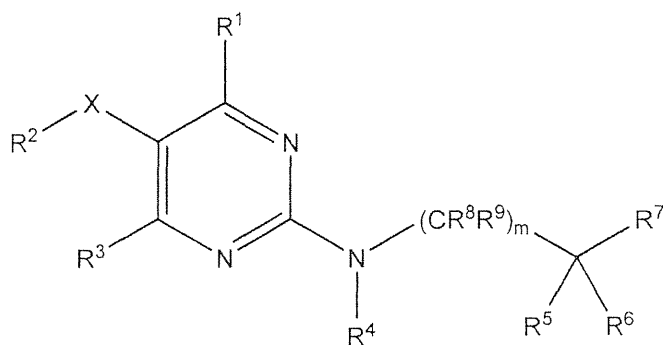
or a pharmaceutically acceptable salt thereof.

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



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from hydrogen, halogen, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C(O)OR^a, C(O)NR^bR^c, OR^a, NR^bR^c, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R² is selected from C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and NR^bR^c, wherein each of the C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, (CH₂)_nOR^a, (CH₂)_nOC(O)R^a, (CH₂)_nOC(O)OR^a, (CH₂)_nOC(O)NR^bR^c, (CH₂)_nNR^bR^c, (CH₂)_nNR^dC(O)R^a, (CH₂)_nNR^dC(O)OR^a, (CH₂)_nNR^dC(O)NR^bR^c, (CH₂)_nNR^dC(O)C(O)NR^bR^c, (CH₂)_nNR^dC(S)R^a, (CH₂)_nNR^dC(S)OR^a, (CH₂)_nNR^dC(S)NR^bR^c, (CH₂)_nNR^dC(NR^e)NR^bR^c, (CH₂)_nNR^dS(O)R^a, (CH₂)_nNR^dSO₂R^a, (CH₂)_nNR^dSO₂NR^bR^c, (CH₂)_nC(O)R^a, (CH₂)_nC(O)OR^a, (CH₂)_nC(O)NR^bR^c, (CH₂)_nC(S)R^a, (CH₂)_nC(S)OR^a, (CH₂)_nC(S)NR^bR^c, (CH₂)_nC(NR^e)NR^bR^c, (CH₂)_nSR^a, (CH₂)_nS(O)R^a, (CH₂)_nSO₂R^a, (CH₂)_nSO₂NR^bR^c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (CH₂)_nC₃₋₈ cycloalkyl, (CH₂)_n3-8 membered heterocycloalkyl, (CH₂)_nC₆₋₁₀ aryl and (CH₂)_n5-10 membered heteroaryl, wherein each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (CH₂)_nC₃₋₈ cycloalkyl, (CH₂)_n3-8 membered heterocycloalkyl, (CH₂)_nC₆₋₁₀ aryl and (CH₂)_n5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R³ is selected from hydrogen, halogen, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C(O)OR^a, C(O)NR^bR^c, OR^a, NR^bR^c, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R⁴ is selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C(O)R^a, C(O)OR^a, C(O)NR^bR^c and SO₂R^a;

R⁵ and R⁶ are each independently selected from hydrogen, halogen, C₁₋₆ alkyl and C₁₋₆ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, C₇₋₁₁ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, C₇₋₁₁ aralkyl, 5-10 membered heteroaryl, C(O)R^g, C(O)OR^g, C(O)NRⁱR^j and SO₂R^g, wherein each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, C₇₋₁₁ 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 C₁₋₆ alkyl;

R^e, at each occurrence, is independently selected from hydrogen, CN, OH, C₁₋₆ alkoxy, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R^f, at each occurrence, is independently selected from halogen, CN, OR^h, OC(O)R^h, OC(O)OR^h, OC(O)NRⁱR^j, NRⁱR^j, NR^dC(O)R^h, NR^dC(O)OR^h, NR^dC(O)NRⁱR^j, NR^dC(O)C(O)NRⁱR^j, NR^dC(S)R^h, NR^dC(S)OR^h, NR^dC(S)NRⁱR^j, NR^dC(NR^e)NRⁱR^j, NR^dS(O)R^h, NR^dSO₂R^h, NR^dSO₂NRⁱR^j, C(O)R^h, C(O)OR^h, C(O)NRⁱR^j, C(S)R^h, C(S)OR^h, C(S)NRⁱR^j, C(NR^e)NRⁱR^j, SR^h, S(O)R^h, SO₂R^h, SO₂NRⁱR^j, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, C₇₋₁₁ aralkyl and 5-10 membered heteroaryl, wherein each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C₆₋₁₀ aryl, C₇₋₁₁ 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, C₃₋₈ cycloalkyl and 3-8 membered heterocycloalkyl;

R^g, at each occurrence, is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl, naphthyl, and C₇₋₁₁ aralkyl, each optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, OH, C₁₋₆ alkoxy, C₁₋₆ alkyl and C₁₋₆ 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 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHC(O)C_{1-6} \text{ alkyl}$, $NHC(O)C_{7-11} \text{ aralkyl}$, $NHC(O)OC_{1-6} \text{ alkyl}$, $NHC(O)OC_{7-11} \text{ aralkyl}$, $OC(O)C_{1-6} \text{ alkyl}$, $OC(O)C_{7-11} \text{ aralkyl}$, $OC(O)OC_{1-6} \text{ alkyl}$, $OC(O)OC_{7-11} \text{ aralkyl}$, $C(O)C_{1-6} \text{ alkyl}$, $C(O)C_{7-11} \text{ aralkyl}$, $C(O)OC_{1-6} \text{ alkyl}$, $C(O)OC_{7-11} \text{ aralkyl}$, 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;

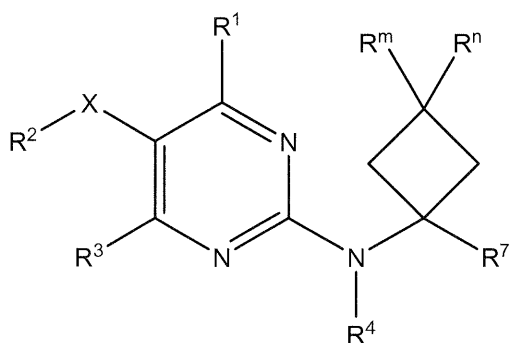
m is 0, 1 or 2;

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

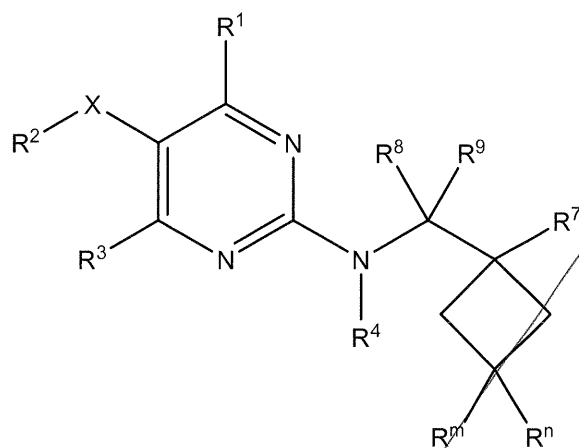
p is 0, 1 or 2; and

q is 0, 1 or 2.

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



Formula V(a)



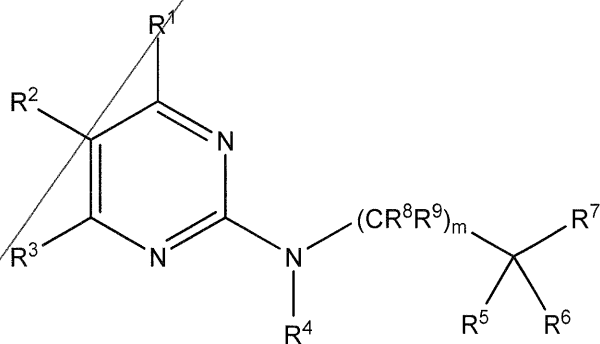
or

Formula V(b)

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

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

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



Formula XII(a).

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