

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 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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, acid maltase deficiency, multiple sclerosis, heart failure, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), and muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.

[0006a] In another aspect, there is provided a 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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, heart failure, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), and muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.

[0006b] In yet another aspect, there is provided a 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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, acid maltase deficiency, multiple sclerosis, heart failure, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), and muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.

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 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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, acid maltase deficiency, multiple sclerosis, heart failure, spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.
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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, acid maltase deficiency, multiple sclerosis, heart failure, spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.
3. The use according to claim 1 or 2, wherein the patient suffers from a disease or condition selected from the group consisting of sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, and acid maltase deficiency.

4. The use according to claim 1 or 2, wherein the patient suffers from a disease or condition selected from the group consisting of multiple sclerosis, heart failure, spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.

5. The use of any one of claims 1 to 4, wherein the patient suffers from diaphragmatic atrophy.

6. The use according to any one of claims 1 to 5, wherein the patient suffers from one or more of diaphragmatic dysfunction, dyspnea, decreased exercise performance, sleep-disordered breathing, constitutional symptoms, hypersomnia, atelectasis, and respiratory failure.

7. The use according to any one of claims 1 to 6, wherein the patient suffers from partial loss of the ability to generate pressure or complete loss of diaphragmatic function.

8. The use of any one of claims 1 to 6, 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.

9. The use according to any one of claims 1 to 6, wherein the patient undertakes an intense physical activity or is in an environment with a reduced partial pressure of oxygen in the air.

10. The use according to 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.

11. 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 sleep-disordered breathing, diaphragmatic atrophy, 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, stroke, asthma, Arnold-Chiari malformation, quadriplegia, poliomyelitis, syringomyelia, tumor compression, idiopathic hyperinflation, botulism, drug use, acid maltase deficiency, multiple sclerosis, heart failure, spinal muscular atrophy (SMA), myasthenia gravis, chronic obstructive pulmonary disease (COPD), muscular dystrophy, neuralgic neuropathy, critical-illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Lambert-Eaton syndrome, myositis, and disuse atrophy.

12. The use of claim 2 or 11, wherein the skeletal muscle is fast skeletal muscle.

13. The use of any one of claims 1 to 12, wherein the chemical entity is 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol, or a pharmaceutically acceptable salt thereof.

14. The use of any one of claims 1 to 12, wherein the chemical entity is 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one, or a pharmaceutically acceptable salt thereof.