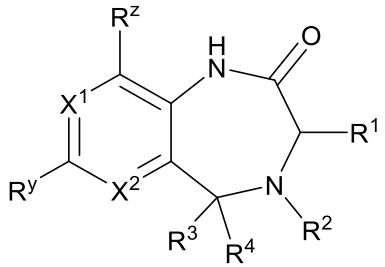
action potentials in the nerve are translated into an impulse in the muscle fiber through release of the neurotransmitter acetylcholine (ACh). ACh triggers a second action potential in the muscle that spreads rapidly along the fiber and into invaginations in the membrane, termed t-tubules. T-tubules are physically connected to Ca^{2+} stores within the sarcoplasmic reticulum (SR) of muscle via the dihydropyridine receptor (DHPR). Stimulation of the DHPR activates a second Ca^{2+} channel in the SR, the ryanodine receptor, to trigger the release of Ca^{2+} from stores in the SR to the muscle cytoplasm where it can interact with the troponin complex to initiate muscle contraction. If muscle stimulation stops, calcium is rapidly taken back up into the SR through the ATP dependent Ca^{2+} pump, sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA).

[0010] Currently, there is limited treatment or no cure for most neuromuscular diseases. Thus, there is a need for the development of new compounds that modulate skeletal muscle contractility. There remains a need for agents that exploit new mechanisms of action and which may have better outcomes in terms of relief of symptoms, safety, and patient mortality, both short-term and long-term and an improved therapeutic index.

SUMMARY

[0011] The ~~invention~~disclosure provides novel compounds that are expected to be used as an active ingredient in a pharmaceutical composition, and in particular, in a pharmaceutical composition for preventing or treating a disease or condition responsive to modulation of the contractility of the skeletal sarcomere. Modulation of the skeletal sarcomere may be modulation, for example, by modulation of the troponin complex of the fast skeletal muscle sarcomere through one or more of fast skeletal myosin, actin, tropomyosin, troponin C, troponin I, and troponin T, and fragments and isoforms thereof.

In an aspect of the present disclosure, there is provided a compound of formula (I):

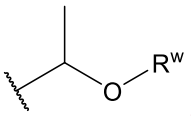


(I),

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently N or C-R^x;

each R^x, R^y, and R^z is independently H, halo, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, or C_{6-20}aryl;

R^1 is C_{3-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, or 

, wherein R^w is optionally substituted C_{1-12}alkyl;

R^2 is:

a) C(O)-R^h, wherein R^h is

(i) optionally substituted amino, optionally substituted C_{1-3}alkoxy, optionally substituted -$C(O)NH_2$, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{6-20}aryl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or

(ii) C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^n, wherein R^n is OH, oxo, halo, cyano, -$C(O)NH_2$, optionally substituted amino, optionally substituted sulfonyl, optionally substituted C_{1-12}alkoxy, optionally substituted C_{6-20}aryloxy, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or

b) C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^m, wherein

R^m is OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-3}alkoxy, C_{6-20}aryloxy, -$C(O)NH_2$, -$C(O)NH(C_{1-12}alkyl)$, -$C(O)N(C_{1-12}alkyl)_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy,-C(O)-(3-15 membered

heterocyclyl), NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, -NH-SO_2-C_{1-12}alkyl, -S(O)-C_{1-12}alkyl, -S(O)$_2$-C_{1-12}alkyl, -S(O)$_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-12}alkyl, C_{1-3}alkoxy, C_{6-20}aryloxy, the C_{1-12}alkyl of -C(O)NH(C_{1-12}alkyl), the C_{1-12}alkyl of -C(O)N(C_{1-12}alkyl)$_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy, the 3-15 membered heterocyclyl of -C(O)-(3-15 membered heterocyclyl), NH_2, the C_{1-12}alkyl of -NH(C_{1-12}alkyl), the C_{1-12}alkyl of -N(C_{1-12}alkyl)$_2$, the C_{1-12}alkyl of -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, the C_{1-12}alkyl of -NH-SO_2-C_{1-12}alkyl, the C_{1-12}alkyl of -S(O)-C_{1-12}alkyl, the C_{1-12}alkyl of -S(O)$_2$-C_{1-12}alkyl, -S(O)$_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl of R^m is further optionally substituted by one or more OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-12}alkoxy, -C(O)NH_2, -C(O)NH(C_{1-12}alkyl), -C(O)N(C_{1-12}alkyl)$_2$, C(O)OH, NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, C_{3-10}cycloalkyl, C_{6-20}aryl, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, or

c) optionally substituted C_{3-10}cycloalkenyl, or

d) optionally substituted 5-20 membered heteroaryl, or

e) optionally substituted 3-15 membered heterocyclyl, or

f) optionally substituted amidinyl, or

g) optionally substituted sulfonyl, or

h) cyano, and

R^3 is H, optionally substituted C_{1-12}alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-C_{1-12}alkoxy; or

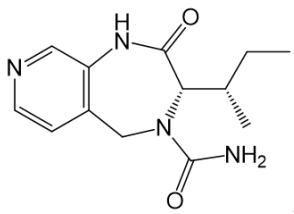
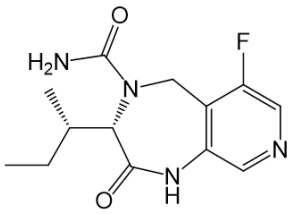
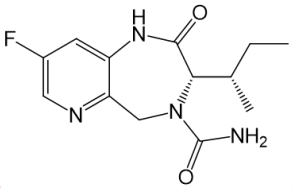
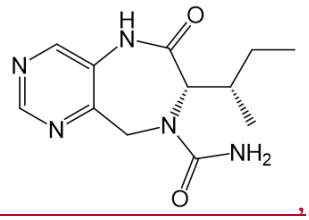
R^2 and R^3 are taken together with the atoms to which they are attached to form a 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl, wherein the 5- or 6-membered

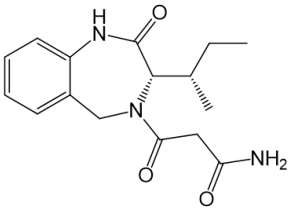
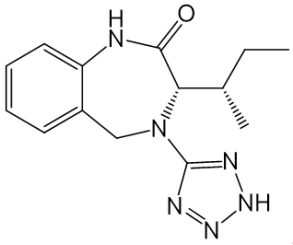
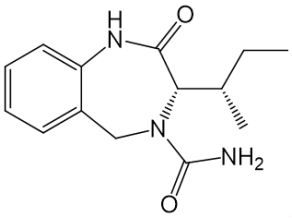
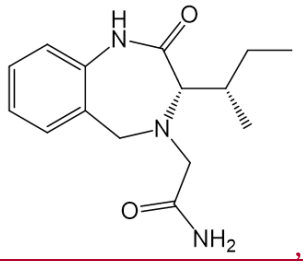
heterocyclyl or 5- or 6-membered heteroaryl independently comprises two or more annular heteroatoms and is independently optionally substituted; and

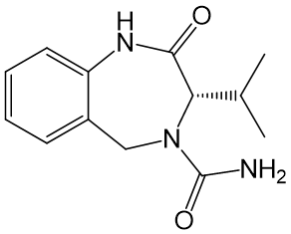
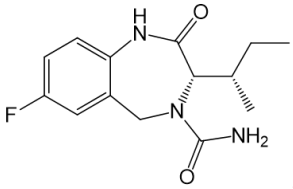
R^4 is absent or is H, optionally substituted C_{1-12}alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-C_{1-12}alkoxy.

In another aspect of the present disclosure, there is provided a compound selected from Table 2, or a pharmaceutically acceptable salt thereof.

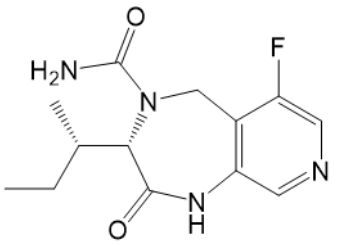
In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

, , , ,

, , , ,

, and , or a pharmaceutically acceptable salt thereof.

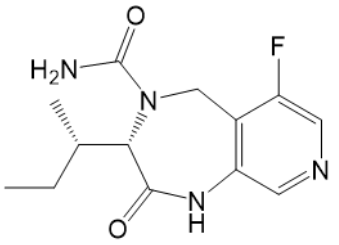
In another aspect of the present disclosure, there is provided a crystalline form of Compound 10:



Compound 10

characterized by having an XRPD pattern comprising peaks at angles 2-theta of 8.26±0.2, 16.47±0.2, 24.36±0.2, and 24.75±0.2 degrees.

In a further aspect of the present disclosure, there is provided a crystalline form of Compound 10:



Compound 10

characterized by having an XRPD pattern comprising peaks at angles 2-theta of 10.16±0.2, 13.86±0.2, 16.60±0.2, and 19.54±0.2 degrees.

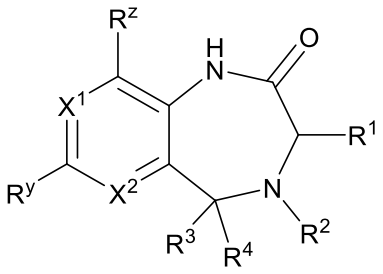
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

In a further aspect of the present disclosure, there is provided a use of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, for the manufacture of a medicament for preventing or treating a disease or condition selected from the group consisting of peripheral vascular disease, peripheral arterial disease, rehabilitation-related deficits, metabolic syndrome, obesity, ventilator-induced muscle weakness, chronic fatigue syndrome, neuromuscular disorders, conditions of muscle wasting,

muscular myopathies, muscle atrophy, fatigue, frailty, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, muscular myopathies, stress urinary incontinence (SUI), mixed urinary incontinence (MUI), fecal incontinence, sarcopenia, chronic obstructive pulmonary disease (COPD), cachexia syndrome, muscle wasting caused by heart failure, cancer, or chronic kidney disease/dialysis, post-spinal cord injury (SCI) muscle dysfunction, post-stroke muscle dysfunction, and facioscapulohumeral muscular dystrophy.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, for use in therapy.

[0012] In one ~~aspect~~example, provided herein is a compound of formula (I):



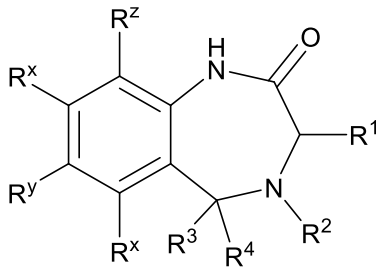
(I),

R^2 and R^3 are taken together with the atoms to which they are attached to form a 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl independently comprises two or more annular heteroatoms and is independently optionally substituted; and

R^4 is absent or is H, optionally substituted $C_{1\text{-}12}$alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-$C_{1\text{-}12}$alkoxy**,**

or any variation or ~~embodiment~~example thereof.

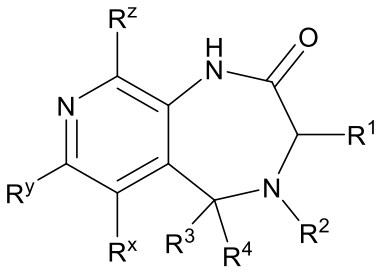
[0013] In another ~~aspect~~example, provided herein is a compound of formula (II):



(II),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x, R^y, R^z, R^1, R^2, R^3, and R^4 are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

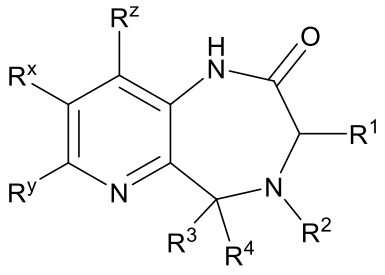
[0014] In another ~~aspect~~example, provided herein is a compound of formula (III):



(III),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x, R^y, R^z, R^1, R^2, R^3, and R^4 are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

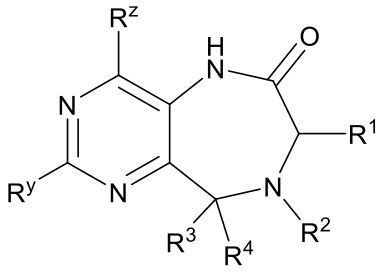
[0015] In another ~~aspect~~example, provided herein is a compound of formula (IV):



(IV),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x, R^y, R^z, R^1, R^2, R^3, and R^4 are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

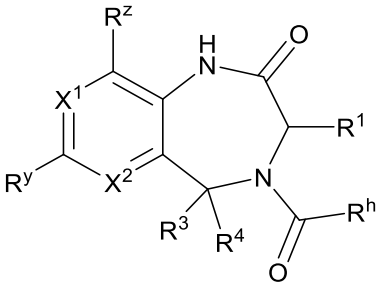
[0016] In another ~~aspect~~example, provided herein is a compound of formula (V):



(V),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^y, R^z, R^1, R^2, R^3, and R^4 are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

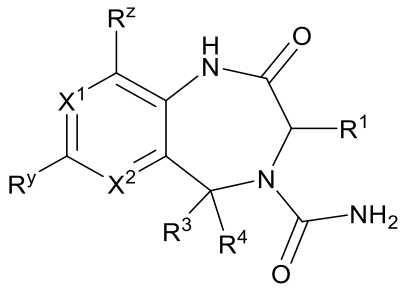
[0017] In another ~~aspect~~example, provided herein is a compound of formula (I-A):



(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, R^y, R^z, R^1, R^3, R^4, and R^h are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

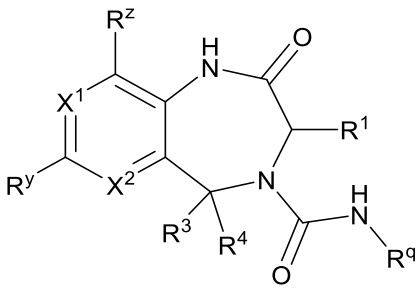
[0018] In a further ~~aspect~~example, provided herein is a compound of (I-B):



(I-B),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, R^y, R^z, R^1, R^3, and R^4 are as defined for the compound of formula (I), or any variation or ~~embodiment~~example thereof.

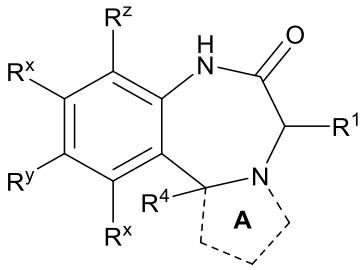
[0019] In a further ~~aspect~~example, provided herein is a compound of (I-C):



(I-C),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, R^y, R^z, R^1, R^3, and R^4 are as defined for the compound of formula (I), and R^q is optionally substituted $C_{1\text{-}12}$alkyl, optionally substituted $C_{3\text{-}10}$cycloalkyl, optionally substituted $C_{6\text{-}20}$aryl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or any variation or ~~embodiment~~example thereof.

[0020] In another ~~aspect~~example, provided herein is a compound of formula (I-D):



(I-D),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x, R^y, R^z, R^1, and R^4 are as defined for the compound of formula (I), and ring A is a 5-membered heterocyclyl or 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl independently comprises two or more annular heteroatoms and is independently optionally substituted, or any variation or ~~embodiment~~example thereof.

[0021] Unless specifically described otherwise, when symbols in one formula in the specification are also used in other formulae, the same symbols denote the same meanings. When the same symbol is used more than once in a given formula, it is to be understood that each instance of that symbol in the formula represents an independently selected chemical moiety and that all instances of the symbol in the formula need not necessarily represent identical chemical moieties.

[0022] In a further ~~aspect~~example, the present ~~invention~~disclosure relates to a pharmaceutical composition comprising one or more of the compounds described herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for preventing or treating various diseases, disorders, and conditions responsive to the modulation of the contractility of the skeletal sarcomere.

[0023] In some ~~aspect~~examples, the present ~~invention~~disclosure relates to methods of preventing or treating frailty associated with old age (termed sarcopenia); cachexia syndromes associated with diseases such as cancer, heart failure, chronic obstructive pulmonary disease (COPD), renal disease, and chronic kidney disease/dialysis; diseases and disorders of the central nervous system (CNS); neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and myasthenia gravis, peripheral neuropathies, Charcot-Marie-Tooth disease, Parkinson's disease, stroke, spinal cord injury, and motor units disorders; muscular myopathies,

including body myositis myopathy, muscular dystrophies (limb girdle, facioscapulohumeral, oculopharyngeal), steroid myopathy, and mitochondrial myopathies; rehabilitation-related deficits: recovery from surgery (e.g., post-surgical muscle weakness), prolonged bed rest, immobilization/disuse atrophy, post-hip fracture recovery, ICU neuromyopathy, post trauma, stroke rehabilitation; Peripheral Vascular Disease (PVD) or Peripheral Arterial Disease (PAD) (e.g., claudication), metabolic syndrome, chronic fatigue syndrome, obesity, and frailty due to aging; post-anesthesia recovery or reversal of neuromuscular blockade; obstructive sleep apnea; chronic fatigue syndrome; metabolic syndrome, metabolic/ischemic disorders, or claudication; obesity; dysfunctions of pelvic floor and urethral/anal sphincter muscles (e.g., urinary incontinence such as stress urinary incontinence (SUI) and mixed urinary incontinence (MUI), and fecal incontinence); post-spinal cord injury (SCI) muscle dysfunction; ventilator-induced muscle weakness; or spinocerebral ataxias or demyelinating diseases, including multiple sclerosis, post-polio syndrome, or any combination of the foregoing, using one or more of the compounds described herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition thereof.

[0024] Additional ~~embodiment~~example~~s~~, features, and advantages of the present disclosure will be apparent from the following detailed description and through practice of the present disclosure.

[0025] For the sake of brevity, the disclosures of publications cited in this specification, including patents, are herein incorporated by reference.

DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1A shows an XRPD pattern of crystalline Form I of Compound 10.

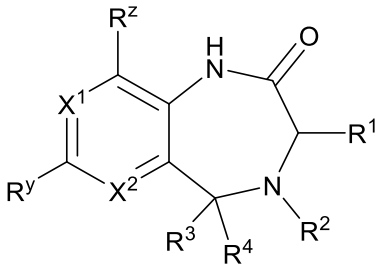
[0027] FIG. 1B shows differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) graphs of crystalline Form I of Compound 10.

[0028] FIG. 2A shows an XRPD pattern of crystalline Form II of Compound 10.

[0029] FIG. 2B shows DSC and TGA graphs of crystalline Form II of Compound 10.

CLAIMS

1. A compound of formula (I):

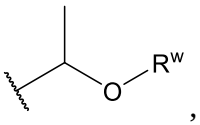


(I),

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently N or C-R^x;

each R^x, R^y, and R^z is independently H, halo, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, or C_{6-20}aryl;

R^1 is C_{3-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, or 

, wherein R^w is optionally substituted C_{1-12}alkyl;

R^2 is:

a) C(O)-R^h, wherein R^h is

(i) optionally substituted amino, optionally substituted C_{1-3}alkoxy, optionally substituted -C(O)NH_2, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{6-20}aryl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or

(ii) C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^n, wherein R^n is OH, oxo, halo, cyano, -C(O)NH_2, optionally substituted amino, optionally substituted sulfonyl, optionally substituted C_{1-12}alkoxy, optionally substituted C_{6-20}aryloxy, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or

b) C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^m, wherein

R^m is OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-}~~$_{12}$~~$_3$alkoxy, C_{6-20}aryloxy, -C(O)NH_2, -C(O)NH(C_{1-12}alkyl), -C(O)N(C_{1-12}alkyl)$_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy,-C(O)-(3-15 membered heterocyclyl), NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, -NH-SO_2-C_{1-12}alkyl, -S(O)-C_{1-12}alkyl, -S(O)$_2$-C_{1-12}alkyl, -S(O)$_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-12}alkyl, C_{1-}~~$_{12}$~~$_3$alkoxy, C_{6-20}aryloxy, the C_{1-12}alkyl of -C(O)NH(C_{1-12}alkyl), the C_{1-12}alkyl of -C(O)N(C_{1-12}alkyl)$_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy, the 3-15 membered heterocyclyl of -C(O)-(3-15 membered heterocyclyl), NH_2, the C_{1-12}alkyl of -NH(C_{1-12}alkyl), the C_{1-12}alkyl of -N(C_{1-12}alkyl)$_2$, the C_{1-12}alkyl of -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, the C_{1-12}alkyl of -NH-SO_2-C_{1-12}alkyl, the C_{1-12}alkyl of -S(O)-C_{1-12}alkyl, the C_{1-12}alkyl of -S(O)$_2$-C_{1-12}alkyl, -S(O)$_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl of R^m is further optionally substituted by one or more OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-12}alkoxy, -C(O)NH_2, -C(O)NH(C_{1-12}alkyl), -C(O)N(C_{1-12}alkyl)$_2$, C(O)OH, NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, C_{3-10}cycloalkyl, C_{6-20}aryl, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, or

c) optionally substituted C_{3-10}cycloalkenyl, or

d) optionally substituted 5-20 membered heteroaryl, or

e) optionally substituted 3-15 membered heterocyclyl, or

f) optionally substituted amidinyl, or

g) optionally substituted sulfonyl, or

h) cyano, and

R^3 is H, optionally substituted C_{1-12}alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-C_{1-12}alkoxy; or

R^2 and R^3 are taken together with the atoms to which they are attached to form a 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl independently comprises two or more annular heteroatoms and is independently optionally substituted; and

R^4 is absent or is H, optionally substituted C_{1-12}alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-C_{1-12}alkoxy.

~~2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of X^1 and X^2 is N.~~

~~3~~2. The compound of claim 1~~ or claim 2~~, or a pharmaceutically acceptable salt thereof, wherein X^1 is N and X^2 is C-R^x.

~~4~~3. The compound of claim 1~~ or claim 2~~, or a pharmaceutically acceptable salt thereof, wherein X^1 is C-R^x and X^2 is N.

~~4~~5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each independently C-R^x.

~~6~~5. The compound of any one of claims 1-~~5~~4, or a pharmaceutically acceptable salt thereof, wherein each R^x is independently H, halo, or C_{3-10}cycloalkyl.

~~7~~6. The compound of any one of claims 1-~~6~~5, or a pharmaceutically acceptable salt thereof, wherein each R^x is independently H or fluoro.

~~8~~7. The compound of claim 1 ~~or claim 2~~, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each N.

~~8~~9. The compound of any one of claims 1-~~7~~8, or a pharmaceutically acceptable salt thereof, wherein R^2 is C(O)-R^h, wherein R^h is

(i) optionally substituted amino, optionally substituted C_{1-3}alkoxy, optionally substituted -$C(O)NH_2$, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{6-20}aryl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl, or

(ii) C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^n, wherein R^n is OH, oxo, halo, cyano, -$C(O)NH_2$, optionally substituted amino, optionally substituted sulfonyl, optionally substituted C_{1-12}alkoxy, optionally substituted C_{6-20}aryloxy, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl.

~~10~~9. The compound of claim ~~9~~8, or a pharmaceutically acceptable salt thereof, wherein R^h is optionally substituted amino.

~~11~~10. The compound of claim ~~9~~8, or a pharmaceutically acceptable salt thereof, wherein R^h is NH_2.

~~12. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^h is amino substituted with one or more R^q, wherein~~

~~R^q is optionally substituted C_{1-12}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-20}aryl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 5-20 membered heteroaryl.~~

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^q is unsubstituted C_{1-12}alkyl, unsubstituted C_{3-10}cycloalkyl, unsubstituted C_{6-20}aryl, unsubstituted 3-15 membered heterocyclyl, or unsubstituted 5-20 membered heteroaryl.

14. The compound of claim 12 or claim 13, or a pharmaceutically acceptable salt thereof, wherein R^q is unsubstituted C_{1-12}alkyl.

15. The compound of any one of claims 12-14, or a pharmaceutically acceptable salt thereof, wherein R^q is unsubstituted methyl.

16. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^h is C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^a, wherein R^a is OH, $-SO_2-C_{1-12}$alkyl, $-SO_2-NH_2$, NH_2, $-NHC(O)-C_{1-12}$alkyl, $-C(O)NH_2$, C_{1-12}alkoxy, C_{6-20}aryloxy, or 3-15 membered heterocyclyl, wherein the C_{1-12}alkoxy, C_{6-20}aryloxy, or 3-15 membered heterocyclyl of R^a is independently further optionally substituted with one or more OH, $-C(O)NH_2$, or C_{6-20}aryl.

17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein R^a is OH, NH_2, or $-C(O)NH_2$.

18. The compound of claim 16 or claim 17, or a pharmaceutically acceptable salt thereof, wherein R^a is $-C(O)NH_2$.

19. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^h is C_{1-3}alkoxy, $-C(O)NH_2$, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein the 3-15 membered heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or more OH, NH_2, or C_{1-12}alkyl, wherein the C_{1-12}alkyl is further optionally substituted with one or more OH.

20. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is heteroaryl optionally substituted with one or more OH, NH_2, C_{1-12}alkyl, or C_{1-12}alkoxy.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl of R^2 is a 5-membered heteroaryl optionally substituted with one or more OH, NH_2, C_{1-12}alkyl, or C_{1-12}alkoxy.

22. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is C_{1-12}alkyl, wherein the C_{1-12}alkyl is unsubstituted or is substituted with one or more R^m, wherein

R^m is OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-12}alkoxy, C_{6-20}aryloxy, -C(O)NH_2, -C(O)NH(C_{1-12}alkyl), -C(O)N(C_{1-12}alkyl)$_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy, -C(O)-(3-15 membered heterocyclyl), NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, -NH-SO_2-C_{1-12}alkyl, -S(O)-C_{1-12}alkyl, -$S(O)_2$-C_{1-12}alkyl, -$S(O)_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-12}alkyl, C_{1-12}alkoxy, C_{6-20}aryloxy, the C_{1-12}alkyl of -C(O)NH(C_{1-12}alkyl), the C_{1-12}alkyl of -C(O)N(C_{1-12}alkyl)$_2$, -C(O)OH, -C(O)-C_{1-12}alkoxy, the 3-15 membered heterocyclyl of -C(O)-(3-15 membered heterocyclyl), NH_2, the C_{1-12}alkyl of -NH(C_{1-12}alkyl), the C_{1-12}alkyl of -N(C_{1-12}alkyl)$_2$, the C_{1-12}alkyl of -NHC(O)-C_{1-12}alkyl, -NHC(O)-NH_2, the C_{1-12}alkyl of -NH-SO_2-C_{1-12}alkyl, the C_{1-12}alkyl of -S(O)-C_{1-12}alkyl, the C_{1-12}alkyl of -$S(O)_2$-C_{1-12}alkyl, -$S(O)_2$-NH_2, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl of R^m is further optionally substituted by one or more OH, halo, cyano, oxo, C_{1-12}alkyl, C_{1-12}alkoxy, -C(O)NH_2, -C(O)NH(C_{1-12}alkyl), -C(O)N(C_{1-12}alkyl)$_2$, C(O)OH, NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, C_{3-10}cycloalkyl, C_{6-20}aryl, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl.

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein R^m is -C(O)NH_2 or OH.

24. The compound of claim 22 or claim 23, or a pharmaceutically acceptable salt thereof, wherein R^m is -C(O)NH_2.

25. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is C_{3-10}cycloalkenyl optionally substituted with one or more R^i, wherein R^i is oxo, NH_2, -NH(C_{1-12}alkyl), -N(C_{1-12}alkyl)$_2$, or 3-15 membered heterocyclyl, wherein the 3-15 membered

~~heterocyclyl of R^i, the C_{1-12}alkyl of the –$NH(C_{1-12}$alkyl) of R^i, or the C_{1-12}alkyl of the –$N(C_{1-12}$alkyl)$_2$ of R^i is independently optionally substituted with one or more OH or C_{1-12}alkoxy.~~

~~26. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is 3-15 membered heterocyclyl optionally substituted with one or more OH, oxo, NH_2, or C_{1-12}alkyl.~~

~~27. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is amidinyl optionally substituted with one or more R^5, wherein R^5 is OH, cyano, C_{1-12}alkyl, –C(O)-C_{1-12}alkyl, –C(O)-C_{1-12}alkoxy, C_{6-20}aryloxy, or –SO_2-C_{1-12}alkyl.~~

~~28. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is sulfonyl optionally substituted with one or more R^4, wherein R^4 is C_{1-12}alkyl, NH_2, –$NH(C_{1-12}$alkyl), –$N(C_{1-12}$alkyl)$_2$, or C_{6-20}aryl, wherein the C_{1-12}alkyl or C_{6-20}aryl of R^4 is independently further optionally substituted with one or more halo or C_{1-12}alkoxy.~~

~~29~~11. The compound of any one of claims 1-~~28~~10, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{3-12}alkyl or C_{3-10}cycloalkyl.

12~~30~~. The compound of any one of claims 1-11~~29~~, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{3-6}alkyl or C_{3-8}cycloalkyl.

13~~31~~. The compound of any one of claims 1-12~~30~~, or a pharmaceutically acceptable salt thereof, wherein R^1 is *sec*-butyl, *i*-propyl, or cyclohexyl.

14~~32~~. The compound of any one of claims 1-13~~31~~, or a pharmaceutically acceptable salt thereof, wherein R^1 is *sec*-butyl.

15~~33~~. The compound of any one of claims 1-14~~32~~, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each independently H.

~~34. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein one of R^3 and R^4 is H, and the other of R^3 and R^4 is optionally substituted C_{1-12}alkyl, optionally substituted -C(O)NH_2, or optionally substituted -C(O)-C_{1-12}alkoxy.~~

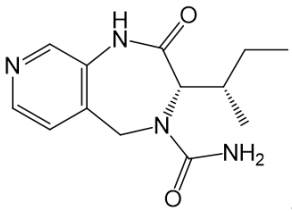
~~35. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each C-R*, and R^2 and R^3 are taken together with the atoms to which they are attached to form a 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heterocyclyl or 5- or 6-membered heteroaryl independently comprises two or more annular heteroatoms and is independently optionally substituted.~~

~~36~~16. The compound of any one of claims 1-~~35~~15, or a pharmaceutically acceptable salt thereof, wherein R^y and R^z are each independently H, halo, or C_{3-10}cycloalkyl.

17~~37~~. The compound of any one of claims 1-16~~36~~, or a pharmaceutically acceptable salt thereof, wherein R^y and R^z are each independently H or fluoro.

18~~38~~. A compound selected from Table 2, or a pharmaceutically acceptable salt thereof.

19~~39~~. A compound selected from the group consisting of: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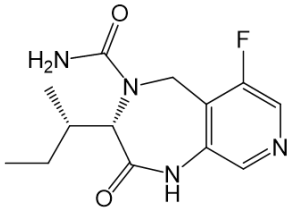
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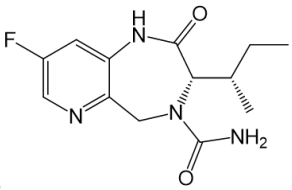
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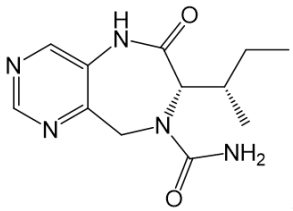
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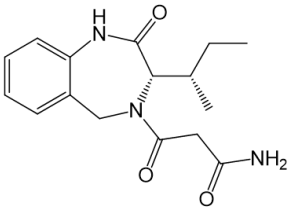
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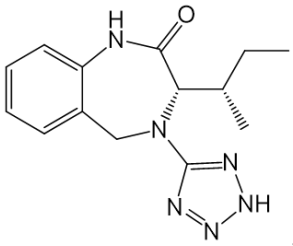
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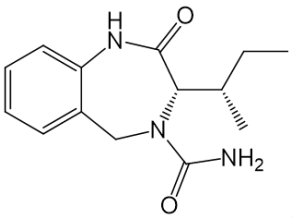
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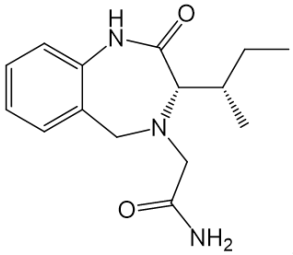
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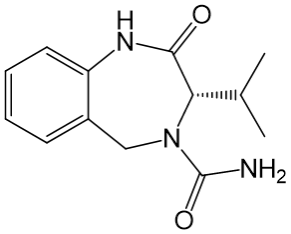
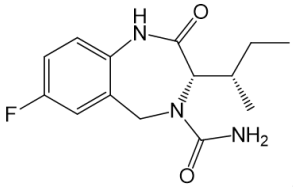
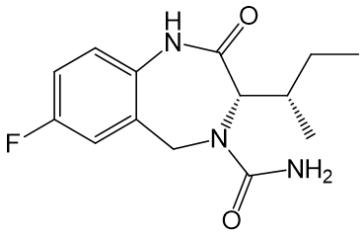

, and

, or a pharmaceutically acceptable salt thereof.

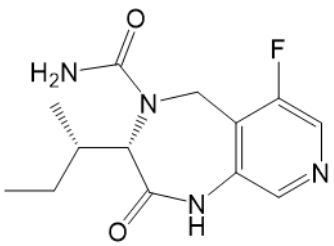
20~~40~~. The compound of claim 1, wherein the compound is Compound 9:



Compound 9,

or a pharmaceutically acceptable salt thereof.

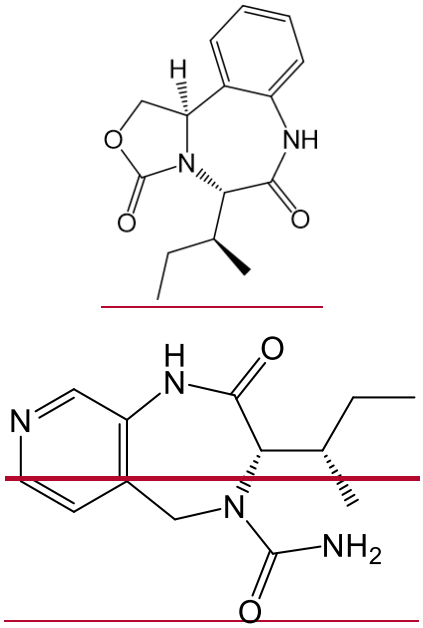
21~~41~~. The compound of claim 1, wherein the compound is Compound 10:



Compound 10,

or a pharmaceutically acceptable salt thereof.

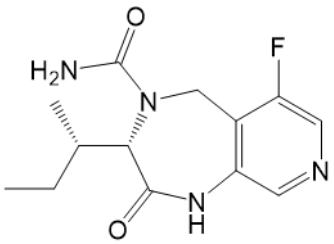
2242. The compound of claim 1, wherein the compound is Compound 3612:



Compound 3612,

or a pharmaceutically acceptable salt thereof.

2343. A crystalline form of Compound 10:



Compound 10

characterized by having an XRPD pattern comprising peaks at angles 2-theta of 8.26±0.2, 16.47±0.2, 24.36±0.2, and 24.75±0.2 degrees.

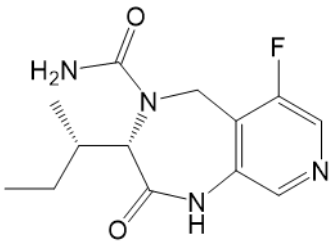
2444. The crystalline form of claim 2343, wherein the XRPD pattern is further characterized by having additional peaks at angles 2-theta of 18.92±0.2, 26.57±0.2, and 31.67±0.2 degrees.

2545. The crystalline form of claim 2343 or 2444, wherein the XRPD pattern is further characterized by having two or more additional peaks at angles 2-theta selected from the group

consisting of 11.84±0.2, 12.49±0.2, 13.08±0.2, 14.11±0.2, 14.38±0.2, 15.71±0.2, 16.96±0.2, 17.20±0.2, 18.05±0.2, 18.39±0.2, 20.29±0.2, 20.68±0.2, 20.99±0.2, 22.13±0.2, 22.67±0.2, 23.65±0.2, 25.30±0.2, 26.23±0.2, 26.97±0.2, 27.30±0.2, 27.66±0.2, 28.07±0.2, 28.36±0.2, 29.06±0.2, 29.58±0.2, 29.98±0.2, 30.54±0.2, 31.04±0.2, 31.33±0.2, and 32.70±0.2 degrees.

2646. The crystalline form of any one of claims 23-2543-45, wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of 10 °C per minute which shows a maximum in endothermic heat flow at a temperature between 238 °C and 250 °C.

2747. A crystalline form of Compound 10:



Compound 10

characterized by having an XRPD pattern comprising peaks at angles 2-theta of 10.16±0.2, 13.86±0.2, 16.60±0.2, and 19.54±0.2 degrees.

2848. The crystalline form of claim 2747, wherein the XRPD is further characterized by having additional peaks at angles 2-theta of 20.70±0.2, 25.38±0.2, 26.51±0.2, and 26.92±0.2 degrees.

2949. The crystalline form of claim 2747 or 2848, wherein the XRPD pattern is further characterized by having two or more additional peaks at angles 2-theta selected from the group consisting of 8.18±0.2, 12.04±0.2, 17.42±0.2, 18.41±0.2, 20.03±0.2, 20.44±0.2, 21.72±0.2, 22.56±0.2, 24.25±0.2, 24.79±0.2, 25.73±0.2, 25.92±0.2, 28.38±0.2, 28.85±0.2, 29.33±0.2, 30.08±0.2, 30.33±0.2, 30.73±0.2, 31.63±0.2, 32.04±0.2, and 32.43±0.2 degrees.

3050. The crystalline form of any one of claims 23-2643-46, wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 1A.

3151. The crystalline form of any one of claims 27-2947-49, wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 2A.

3252. The crystalline form of any one of claims 23-2643-46 or 3050, wherein the crystalline form is characterized by a differential scanning calorimetry trace substantially in accordance with that shown in FigureFIG. 1B.

3353. A pharmaceutical composition comprising a compound of any one of claims 1-2242, or a pharmaceutically acceptable salt thereof, or a crystalline form of any one of claims 43-52, and a pharmaceutical carrier.

54. The pharmaceutical composition of claim 53, wherein the pharmaceutical composition is formulated for oral, sublingual, subcutaneous, parenteral, intravenous, intranasal, topical, transdermal, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal, or intraocular administration.

55. A method for preventing or treating a disease or condition selected from the group consisting of peripheral vascular disease, peripheral arterial disease, rehabilitation-related deficits, metabolic syndrome, obesity, ventilator-induced muscle weakness, chronic fatigue syndrome, neuromuscular disorders, conditions of muscle wasting, muscular myopathies, muscle atrophy and fatigue, and frailty, in a subject, comprising administering to the subject an effective amount of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53.

56. A method for preventing or treating a disease or condition selected from the group consisting of amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, and muscular myopathies, in a subject, comprising administering to the subject an effective amount of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53.

~~57. A method for preventing or treating a disease or condition selected from the group consisting of stress urinary incontinence (SUI), mixed urinary incontinence (MUI), fecal incontinence, frailty, sarcopenia, chronic obstructive pulmonary disease (COPD), cachexia syndrome, muscle wasting caused by heart failure, cancer, or chronic kidney disease/dialysis, post-spinal cord injury (SCI) muscle dysfunction, and post-stroke muscle dysfunction, in a subject, comprising administering to the subject an effective amount of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53.~~

~~58~~34. The use of the compound of any one of claims 1-~~42~~22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim ~~53~~33, for the manufacture of a medicament for preventing or treating a disease or condition selected from the group consisting of peripheral vascular disease, peripheral arterial disease, rehabilitation-related deficits, metabolic syndrome, obesity, ventilator-induced muscle weakness, chronic fatigue syndrome, neuromuscular disorders, conditions of muscle wasting, muscular myopathies, muscle atrophy, ~~and~~ fatigue, frailty, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, muscular myopathies, stress urinary incontinence (SUI), mixed urinary incontinence (MUI), fecal incontinence, sarcopenia, chronic obstructive pulmonary disease (COPD), cachexia syndrome, muscle wasting caused by heart failure, cancer, or chronic kidney disease/dialysis, post-spinal cord injury (SCI) muscle dysfunction, post-stroke muscle dysfunction, and facioscapulohumeral muscular dystrophy~~and frailty in a subject~~.

35. The use of claim 34, wherein the disease or condition is facioscapulohumeral muscular dystrophy.

36. A compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 33, for use in therapy.

~~59. The use of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53, for the manufacture of a medicament for preventing or treating a disease or condition selected from the group consisting of amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, and muscular myopathies in a subject.~~

~~60. The use of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53, for the manufacture of a medicament for preventing or treating a disease or condition selected from the group consisting of stress urinary incontinence (SUI), mixed urinary incontinence (MUI), fecal incontinence, frailty, sarcopenia, chronic obstructive pulmonary disease (COPD), cachexia syndrome, muscle wasting caused by heart failure, cancer, or chronic kidney disease/dialysis, post-spinal cord injury (SCI) muscle dysfunction, and post-stroke muscle dysfunction in a subject.~~

~~61. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53, for use in preventing or treating a disease or condition selected from the group consisting of peripheral vascular disease, peripheral arterial disease, rehabilitation-related deficits, metabolic syndrome, obesity, ventilator-induced muscle weakness, chronic fatigue syndrome, neuromuscular disorders, conditions of muscle wasting, muscular myopathies, muscle atrophy and fatigue, and frailty in a subject.~~

~~62. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53, for use in preventing or treating a disease or condition selected from the group consisting of amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis, and muscular myopathies in a subject.~~

~~63. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53, for use in preventing or treating a disease or condition selected from the group consisting of stress urinary incontinence (SUI), mixed urinary incontinence (MUI), fecal incontinence, frailty, sarcopenia, chronic obstructive pulmonary disease (COPD), cachexia syndrome, muscle wasting caused by heart failure, cancer, or chronic kidney disease/dialysis, post-spinal cord injury (SCI) muscle dysfunction, and post-stroke muscle dysfunction in a subject.~~