PYRIDAZINONE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of US Provisional Application Serial Number 62/756,539 filed November 6, 2018, which is hereby incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

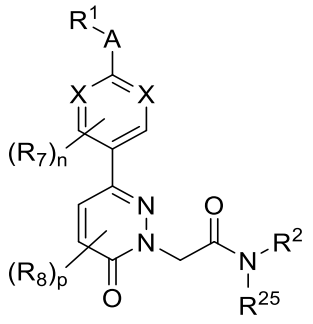
[0002] Skeletal muscle is the largest organ system in the human body, serving two primary purposes. The first is force production to enable muscle contraction, locomotion, and postural maintenance; the second is glucose, fatty acid and amino acid metabolism. The contraction of skeletal muscle during every-day activity and exercise is naturally connected to muscle stress, breakdown and remodeling which is important for muscle adaptation. In individuals with neuromuscular conditions, such as Duchenne Muscular Dystrophy (DMD), muscle contractions lead to continued rounds of amplified muscle breakdown that the body struggles to repair. Eventually, as patients age, a pathophysiological process emerges that leads to excess inflammation, fibrosis, and fatty deposit accumulation in the muscle, portending a steep decline in physical function and contribution to mortality.

[0003] DMD is a genetic disorder affecting skeletal muscle and is characterized by progressive muscle degeneration and weakness. There remains a need for treatments that reduce muscle breakdown in patients with neuromuscular conditions such as DMD.

SUMMARY

[0004] The disclosure provides compound and salts thereof for use in treating disease. In certain examples, the disclosure provides a compound of Formula (I'), (I), (Ia), (Ib), (Ic), (Id), (II'), (II), (III), and (III') pharmaceutical compositions thereof as well as methods of use in the treatment of disease.

[0005] In certain examples, disclosed herein is a compound or a pharmaceutically acceptable salt thereof, represented by Formula (I'):



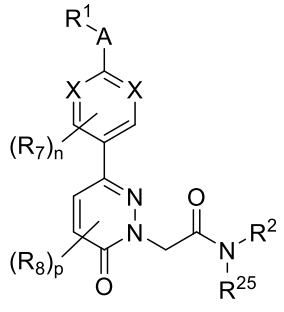
(I');

alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

n is 0, 1, or 2; and

p is 0, 1, or 2.

[0005a] In an aspect, there is provided a compound represented by Formula (I'):



(I');

or a salt thereof, wherein:

each X is independently selected from C(R^3), N, and N^+(-O^-), wherein at least one X is N or N^+(-O^-);

A is selected from -O-, -NR^4-, -CR^5R^6-, -C(O)-, -S-, -S(O)-, and -$S(O)_2$-;

R^1 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -$C(O)N(R^{10})_2$, -$N(R^{10})C(O)R^{10}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$N(R^{10})C(O)N(R^{10})_2$, -$OC(O)N(R^{10})_2$, -$N(R^{10})C(O)OR^{10}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -NO_2, =O, =S, =$N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -$C(O)N(R^{10})_2$, -$N(R^{10})C(O)R^{10}$, -$N(R^{10})C(O)N(R^{10})_2$, -$OC(O)N(R^{10})_2$, -$N(R^{10})C(O)OR^{10}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -NO_2, =O, =S, =$N(R^{10})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with one or more R^9; or

R^1 together with R^5 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9; or R^1 together with R^4 form a 3- to 10-

membered heterocycle, wherein the 3- to 10- membered heterocycle is optionally substituted with one or more R^9;

R^{25} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{25} together with R^2 form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^2 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -C(O)N(R^{10})$_2$, -N(R^{10})C(O)R^{10}, -N(R^{10})C(O)N(R^{10})$_2$, -OC(O)N(R^{10})$_2$, -N(R^{10})C(O)OR^{10}, -C(O)OR^{10}, -OC(O)R^{10}, -S(O)R^{10}, -$S(O)_2R^{10}$, $-NO_2$, =O, =S, =N(R^{10}), -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -C(O)N(R^{10})$_2$, -N(R^{10})C(O)R^{10}, -N(R^{10})C(O)N(R^{10})$_2$, -OC(O)N(R^{10})$_2$, -N(R^{10})C(O)OR^{10}, -C(O)OR^{10}, -OC(O)R^{10}, -S(O)R^{10}, -$S(O)_2R^{10}$, $-NO_2$, =O, =S, =N(R^{10}), –CN, C_{1-6} alkyl, and C_{3-10} carbocycle, wherein the C_{1-6} alkyl, and C_{3-10} carbocycle are optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, $-NO_2$, and –CN; or

R^2 together with R^{25} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^3, R^5, and R^6 are each independently selected from:

hydrogen, halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, $-NO_2$, and -CN; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, $-NO_2$, and -CN; or

R^5 together with R^1 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9;

R^4 is selected from:

hydrogen; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; or

R^4 together with R^1 form a 3- to 10-membered heterocycle, which is optionally substituted with one or more R^9;

R^7 and R^8 are each independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN;

each R^9 is independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, and -CN; and

C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, and -CN;

each R^{10} is independently selected from:

hydrogen; and

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

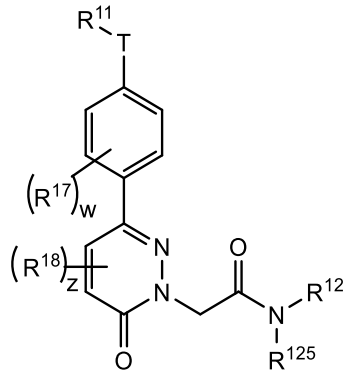
C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

n is 0, 1, or 2; and p is 0, 1, or 2.

[0005b] In another aspect, there is provided a pharmaceutical composition comprising a compound or salt as defined above and a pharmaceutically acceptable excipient.

[0005c] In another aspect, there is provided the use of the pharmaceutical composition as defined above the manufacture of a medicament for the treatment of neuromuscular condition.

[0006] In certain aspects, the disclosure provides a compound represented by Formula (II'):



(II');

or a salt thereof, wherein:

T is selected from -O-, -NR^{14}-, -$CR^{15}R^{16}$-, -C(O)-, -S-, -S(O)-, and -$S(O)_2$;

R^{11} is selected from acetyl and C_{1-5} haloalkyl;

R^{125} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{125} together with R^{12} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^{12} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{20}, -SR^{10}, -N(R^{20})$_2$, -C(O)R^{20}, -C(O)N(R^{20})$_2$, -N(R^{20})C(O)R^{20}, -N(R^{20})C(O)N(R^{20})$_2$, -OC(O)N(R^{20})$_2$, -N(R^{20})C(O)OR^{20}, -C(O)OR^{20}, -OC(O)R^{20}, -S(O)R^{20}, -$S(O)_2R^{20}$, -NO_2, =O, =S, =N(R^{20}), and -CN; and

C_1 alkyl substituted with C_{3-10} carbocycle or 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{19}; and

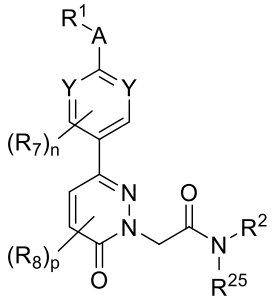
C_{3-10} carbocycle, optionally substituted with one or more R^{19}; or

(Ic), (Id), (II'), (II), (III'), (III) or (IIIa). In certain examples, the disclosure provides a method of inhibiting muscle myosin II comprising administering to a subject in need thereof a compound or salt of any one of Formula (I'), (I), (Ia), (Ib), (Ic), (Id), (II'), (II), (III'), (III) or (IIIa).

[0011a] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound or salt as disclosed herein and a pharmaceutically acceptable excipient.

[0011b] In one aspect, the disclosure provides a use of the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of neuromuscular condition.

[0011c] In one aspect, the disclosure provides a use of a compound or salt of any one of Formula (III'):



(III');

or a salt thereof in the manufacture of a medicament for treating activity-induced muscle damage, a neuromuscular condition, or a movement disorder,

wherein the neuromuscular condition is selected from Duchenne Muscular Dystrophy, Becker muscular dystrophy, myotonic dystrophy 1, myotonic dystrophy 2, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, limb girdle muscular dystrophy, tendinitis, and carpal tunnel syndrome;

wherein the movement disorder is selected from muscle spasticity associated with multiple sclerosis; Parkinson's disease; Alzheimer's disease; cerebral palsy; injury; and a traumatic event, wherein the traumatic event is selected from stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, and amyotrophic lateral sclerosis;

wherein:

each Y is independently selected from $C(R^3)$, N, and $N^+(-O^-)$;

A is absent or selected from -O-, $-NR^4-$, $-CR^5R^6-$, -C(O)-, -S-, -S(O)-, and $-S(O)_2-$;

R^1 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -$C(O)N(R^{10})_2$, -$N(R^{10})C(O)R^{10}$, -$N(R^{10})C(O)N(R^{10})_2$, -$OC(O)N(R^{10})_2$, -$N(R^{10})C(O)OR^{10}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -NO_2, =O, =S, =$N(R^{10})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and

C_{2-6} alkynyl are each optionally substituted with one or more R^9; or

R^1 together with R^5 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9; or R^1 together with R^4 form a 3- to 10- membered heterocycle, wherein the 3- to 10- membered heterocycle is optionally substituted with one or more R^9; and

when A is absent, R^1 is additionally selected from H, and halogen;

R^{25} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{25} together with R^2 form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -$NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^2 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -$C(O)N(R^{10})_2$, -$N(R^{10})C(O)R^{10}$, -$N(R^{10})C(O)N(R^{10})_2$, -$OC(O)N(R^{10})_2$, -$N(R^{10})C(O)OR^{10}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -NO_2, =O, =S, =$N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -$C(O)N(R^{10})_2$, -$N(R^{10})C(O)R^{10}$, -$N(R^{10})C(O)N(R^{10})_2$, -$OC(O)N(R^{10})_2$, -$N(R^{10})C(O)OR^{10}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -NO_2, =O, =S, =$N(R^{10})$, –CN, C_{1-6} alkyl, and C_{3-10} carbocycle, wherein the C_{1-6} alkyl, and C_{3-10} carbocycle are optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -NO_2, and –CN; or

R^2 together with R^{25} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^3, R^5, and R^6 are each independently selected from:

hydrogen, halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; or R^5 together with R^1 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9;

R^4 is selected from:

hydrogen; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; or

R^4 together with R^1 form a 3- to 10-membered heterocycle, which is optionally substituted with one or more R^9;

R^7 and R^8 are each independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN;

each R^9 is independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, =N(R^{10}), and -CN; and

C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, =N(R^{10}), and -CN;

each R^{10} is independently selected from:

hydrogen; and

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$,

=O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

n is 0, 1, or 2; and

p is 0, 1, or 2, and

wherein the medicament is to be administered to a subject in need thereof.

[0011d] In one aspect, the disclosure provides the pharmaceutical composition as described herein for use in therapy.

INCORPORATION BY REFERENCE

[0011] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

[0013] FIG.1 depicts excessive contraction-induced injuries, which precede the inflammation and irreversible fibrosis that characterizes late-stage DMD pathology;

[0014] FIG.2 N-benzyl-p-tolyl-sulfonamide (BTS), an inhibitor of fast-fiber skeletal muscle myosin, has been shown to protect muscles from pathological muscle derangement in embryos from zebrafish model of DMD;

[0015] FIG.3 depicts the force decrease pre injury at 100Hz for various compounds of the disclosure;

[0016] FIG.4 depicts the post injury force decrease at 175 Hz for various compounds of the disclosure;

[0017] FIG.5 depicts mid lengthening force drop for various compounds of the disclosure; and

[0018] FIG.6 depicts the TA mass increase after injury for various compounds of the disclosure.

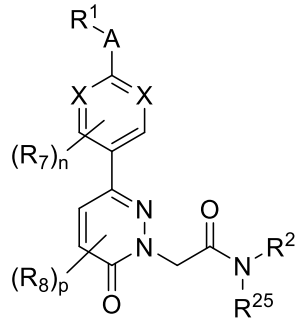
DETAILED DESCRIPTION OF THE INVENTION

[0019] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I'):



(I');

or a salt thereof, wherein:

each X is independently selected from $C(R^3)$, N, and $N^+(-O^-)$, wherein at least one X is N or $N^+(-O^-)$;

A is selected from -O-, $-NR^4-$, $-CR^5R^6-$, -C(O)-, -S-, -S(O)-, and $-S(O)_2-$;

R^1 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with one or more R^9; or

R^1 together with R^5 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9; or R^1 together with R^4 form a 3- to 10- membered heterocycle,

wherein the 3- to 10- membered heterocycle is optionally substituted with one or more R^9;

R^{25} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{25} together with R^2 form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^2 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, –CN, C_{1-6} alkyl, and C_{3-10} carbocycle, wherein the C_{1-6} alkyl, and C_{3-10} carbocycle are optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and –CN; or

R^2 together with R^{25} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^3, R^5, and R^6 are each independently selected from:

hydrogen, halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; or

R^5 together with R^1 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9;

R^4 is selected from:

hydrogen; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN; or

R^4 together with R^1 form a 3- to 10-membered heterocycle, which is optionally substituted with one or more R^9;

R^7 and R^8 are each independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and -CN;

each R^9 is independently selected from:

halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, and -CN; and

C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, and -CN;

each R^{10} is independently selected from:

hydrogen; and

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -

NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

n is 0, 1, or 2; and

p is 0, 1, or 2.

2. The compound or salt of claim 1, wherein A is selected from -O-, -NR^4-, and -CR^5R^6-.

3. The compound or salt of claim 1, wherein R^1 is selected from:

C_{1-6} alkyl, optionally substituted with one to three substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, =O, =S, =NH, =N(C_{1-3} alkyl), -CN, C_{3-6} carbocycle, and 3- to 6-membered heterocycle, wherein the C_{3-6} carbocycle or 3- to 6-membered heterocycle is optionally substituted with one or more R^9; and

R^1 is selected from C_{3-8} carbocycle, and 3- to 8-membered heterocycle containing one to three heteroatoms, wherein the C_{3-8} carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more R^9; or

R^1 together with R^4 form a 4- to 9-membered heterocycle, optionally substituted with one or more R^9, wherein the 4- to 9-membered heterocycle is selected from monocyclic ring, bridged ring, and spiro-cyclic ring, optionally containing one or two additional heteroatoms; or

R^1 together with R^5 form a C_{3-6} cycloalkyl, optionally substituted with one or more R^9.

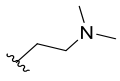
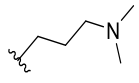
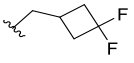
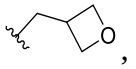
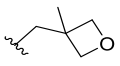
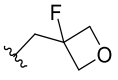
4. The compound or salt of claim 1, wherein R^1 is selected from:

C_{1-4} alkyl, optionally substituted with one to three substituents independently selected from halogen, -O-C_{1-3} haloalkyl, C_{4-6} cycloalkyl, and 4-membered saturated heterocycle containing one heteroatom, wherein the C_{4-6} cycloalkyl or 4-membered saturated heterocycle is optionally substituted with one to three substituents independently selected from halogen and C_{1-3} alkyl; and

C_{4-6} cycloalkyl, C_{5-8} bridged cycloalkyl, phenyl, and 4- to 6-membered saturated heterocycle containing one heteroatom, wherein the C_{4-6} cycloalkyl, C_{5-8} bridged cycloalkyl, phenyl, and 4- to 6-membered saturated heterocycle are each optionally substituted with one to three substituents independently selected from halogen, -OH, -O-C_{1-3} alkyl, -O-C_{1-3} haloalkyl, C_{1-3} alkyl, and C_{1-3} hydroxyalkyl; or

R^1 together with R^4 form a 4- to 7-membered heterocycle selected from azetidine, pyrrolidine, piperidine, morpholine, spiro-azetidine, bridged piperidine, and bridged morpholine, each optionally substituted with one to three R^9, wherein the spiro-azetidine, bridged piperidine, and bridged morpholine each optionally contains an additional heteroatom; and wherein each R^9 is independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -O-C_{1-3} haloalkyl, wherein the C_{1-3} alkyl is optionally further substituted with one -O-C_{1-3} haloalkyl; or

R^1 together with R^5 form a C_{3-6} cycloalkyl.

5. The compound or salt of claim 1, wherein R^1 is selected from C_{1-6} alkyl, optionally substituted with one to three substituents independently selected from halogen, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -NO_2, =O, =S, =NH, =N(C_{1-3} alkyl), -CN, C_{3-6} carbocycle, and 3- to 6-membered heterocycle, wherein the C_{3-6} carbocycle or 3- to 6-membered heterocycle is optionally substituted with one or more R^9.
6. The compound or salt of claim 1, wherein R^1 is selected from -CH_3, -$CH(CH_3)_2$, -$CH_2CH_2CH_3$, -$C(CH_3)_3$, -CHF_2, -CF_3, -CH_2CF_3, $CH_2CH_2CF_3$, -CH_2CH_2-O-CF_3, , , , , , and .
7. The compound or salt of claim 1, wherein R^1 is selected from C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein the C_{3-8} carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more R^9.
8. The compound or salt of claim 1, wherein R^1 and R^4 together with the N atom to which they are attached form a 4- to 9-membered heterocycle, optionally substituted with one or more R^9; wherein the 4- to 9-membered heterocycle is selected from monocyclic, bridged, and spiro-cyclic.
9. The compound or salt of claim 1, wherein R^2 is selected from:

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, aryl, and 5- to 6-membered heteroaryl, wherein the aryl and 5- to 6-membered heteroaryl are each optionally substituted with one or more R^9; and

a saturated C_{3-8} carbocycle, optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, and aryl; or

R^2 and R^{25} together with the N atom to which they are attached form a 4- to 6-membered ring, optionally substituted with one or more R^9.

10. The compound or salt of claim 1, wherein R^2 is selected from:

C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halogen, -CN, and phenyl, wherein the phenyl is optionally substituted with one, or two, or three halogens; and

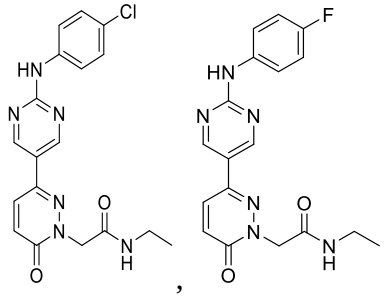
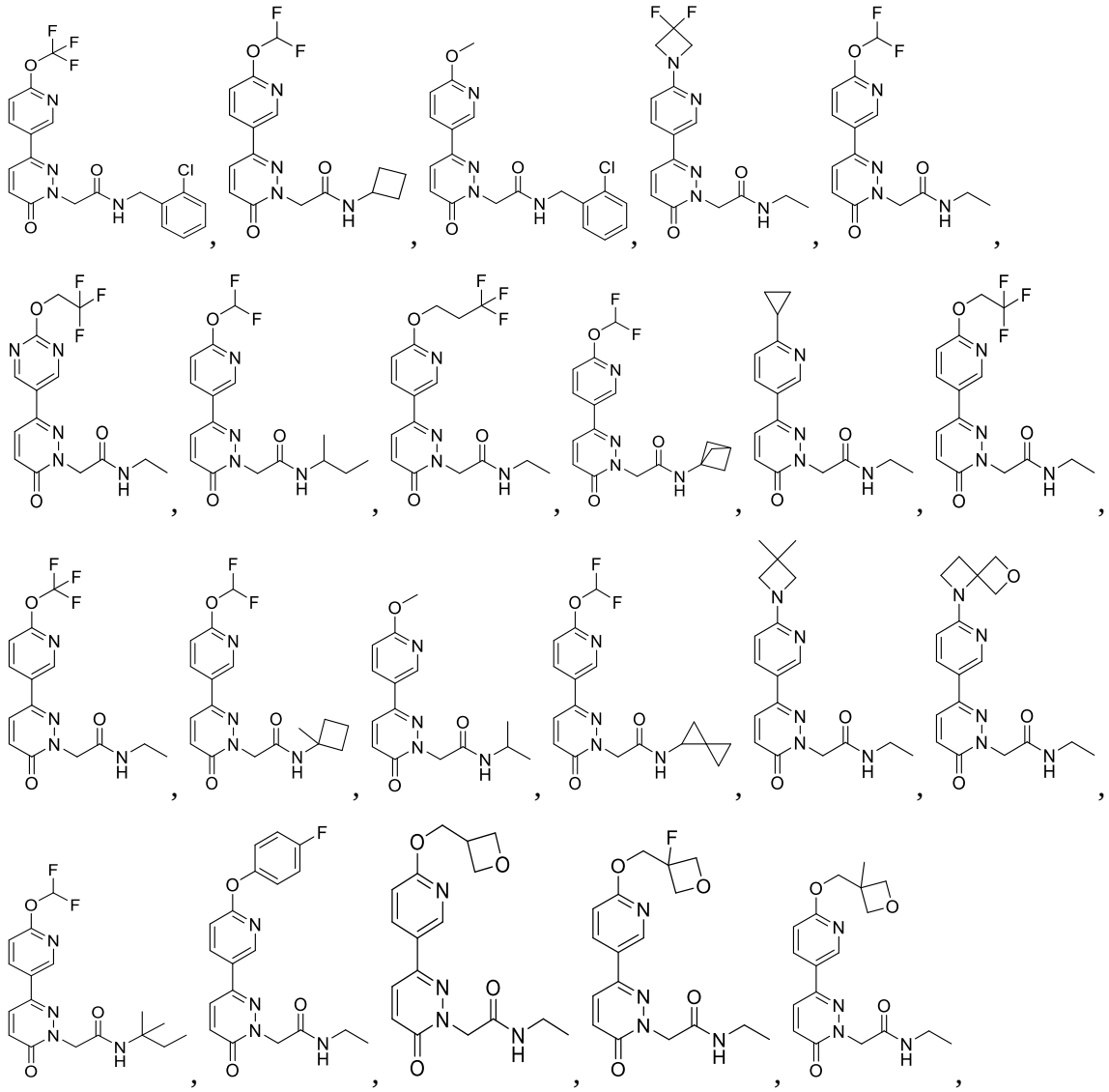
C_{3-4} cycloalkyl,  , and  , each optionally substituted with C_{1-3} alkyl or phenyl; or

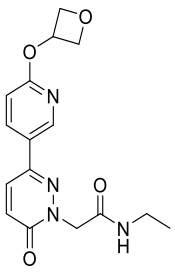
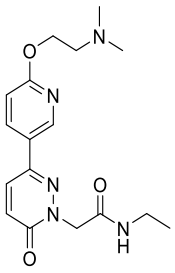
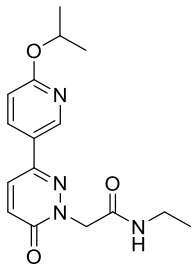
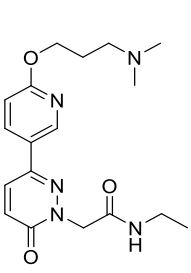
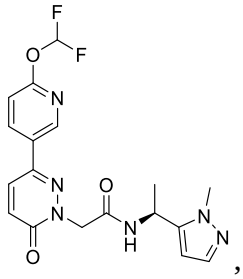
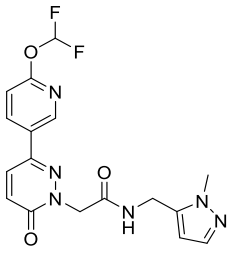
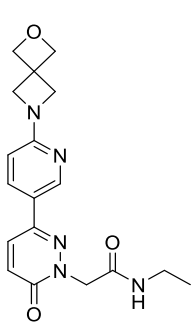
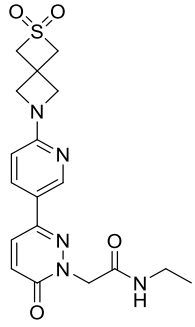
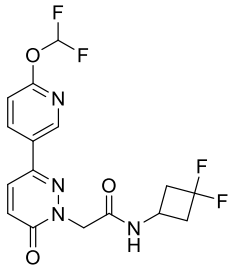
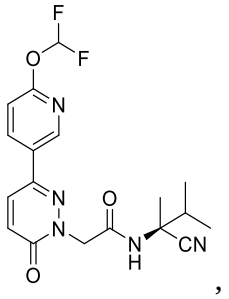
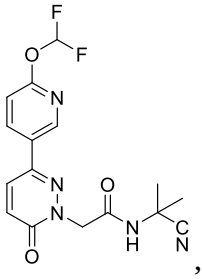
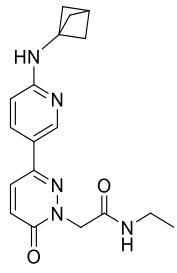
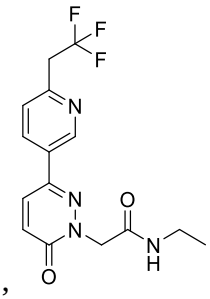
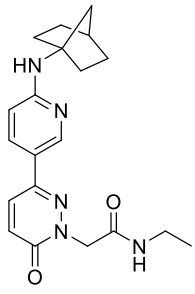
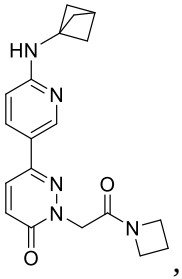
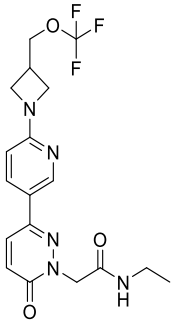
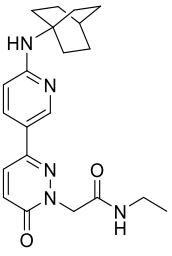
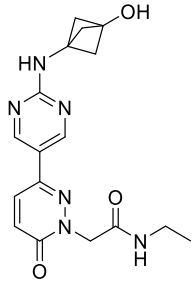
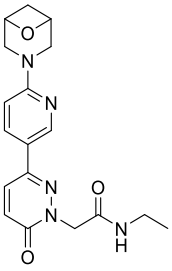
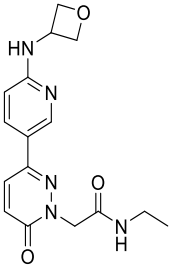
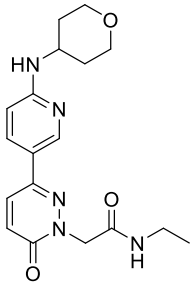
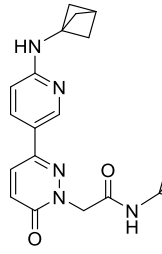
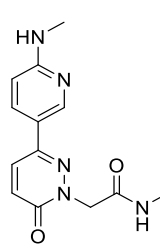
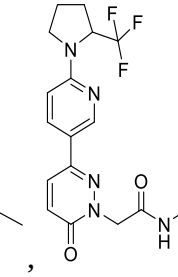
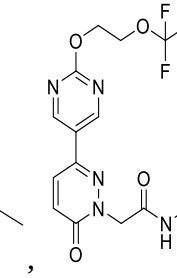
R^2 and R^{25} together with the N atom to which they are attached form azetidinyl.

11. The compound or salt of claim 1, wherein R^2 is C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, aryl, and 5- to 6-membered heteroaryl containing one to three heteroatoms, wherein the aryl and 5- to 6-membered heteroaryl are each optionally substituted with one or more R^9.
12. (Previously Presented) The compound or salt of claim 1, wherein R^2 together with R^{25} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl.
13. The compound or salt of claim 1, wherein R^2 is C_{1-5} alkyl, optionally substituted with one to three substituents independently selected from halogen, -CN, and phenyl, wherein the phenyl is optionally substituted with one, or two, or three halogens.

14. The compound or salt of claim 1, wherein R^2 is a saturated C_{3-8} carbocycle, optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, and C_{4-6} carbocycle.

15. The compound or salt of claim 1, wherein n is 0 and p is 0.

16. The compound of claim 1, selected from: , 


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

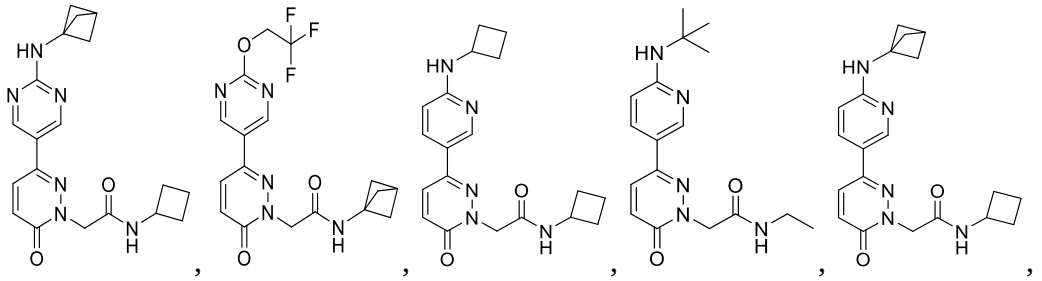
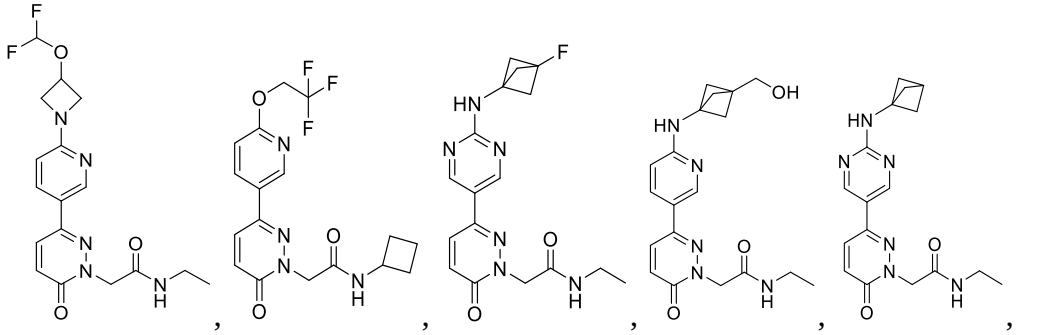
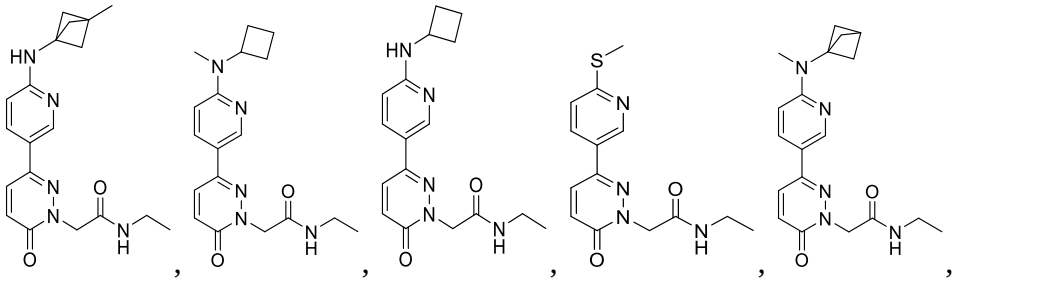
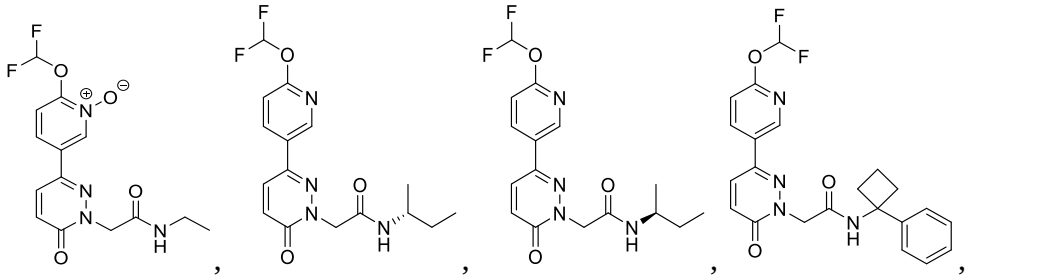
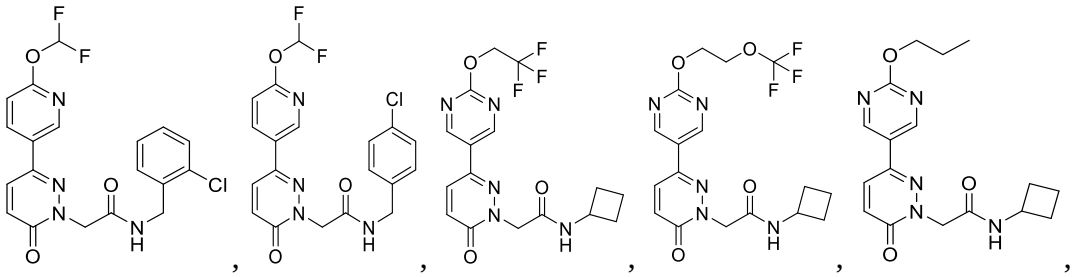
,

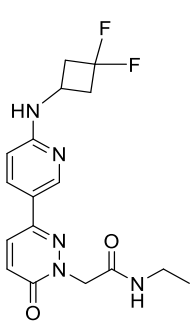
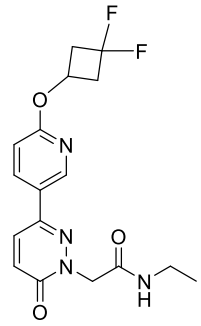
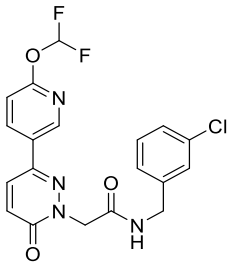
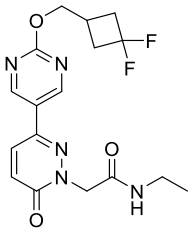
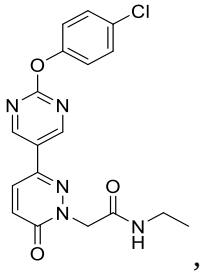
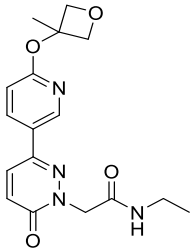
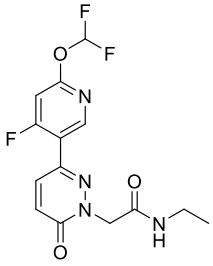
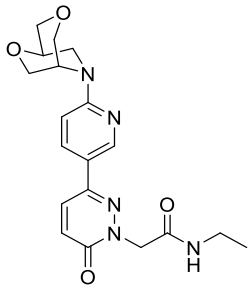
,

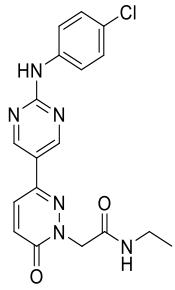
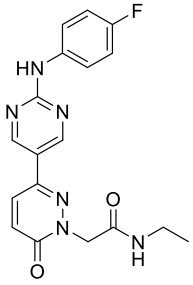
,

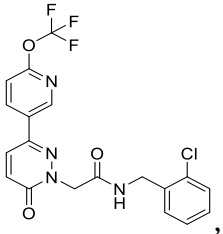
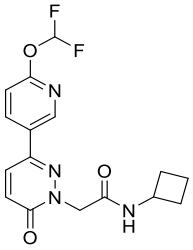
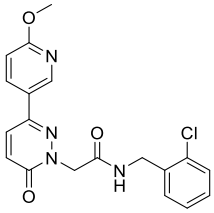
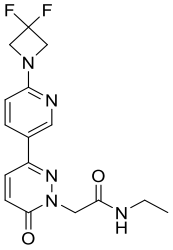
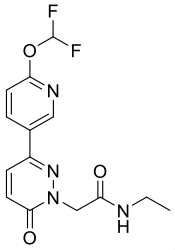
,

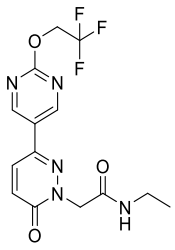
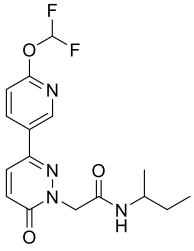
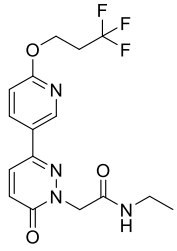
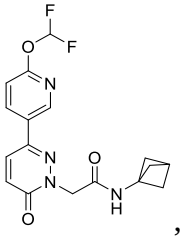
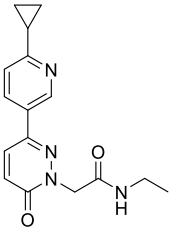
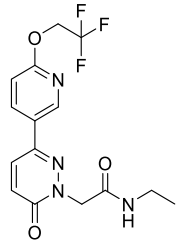
,

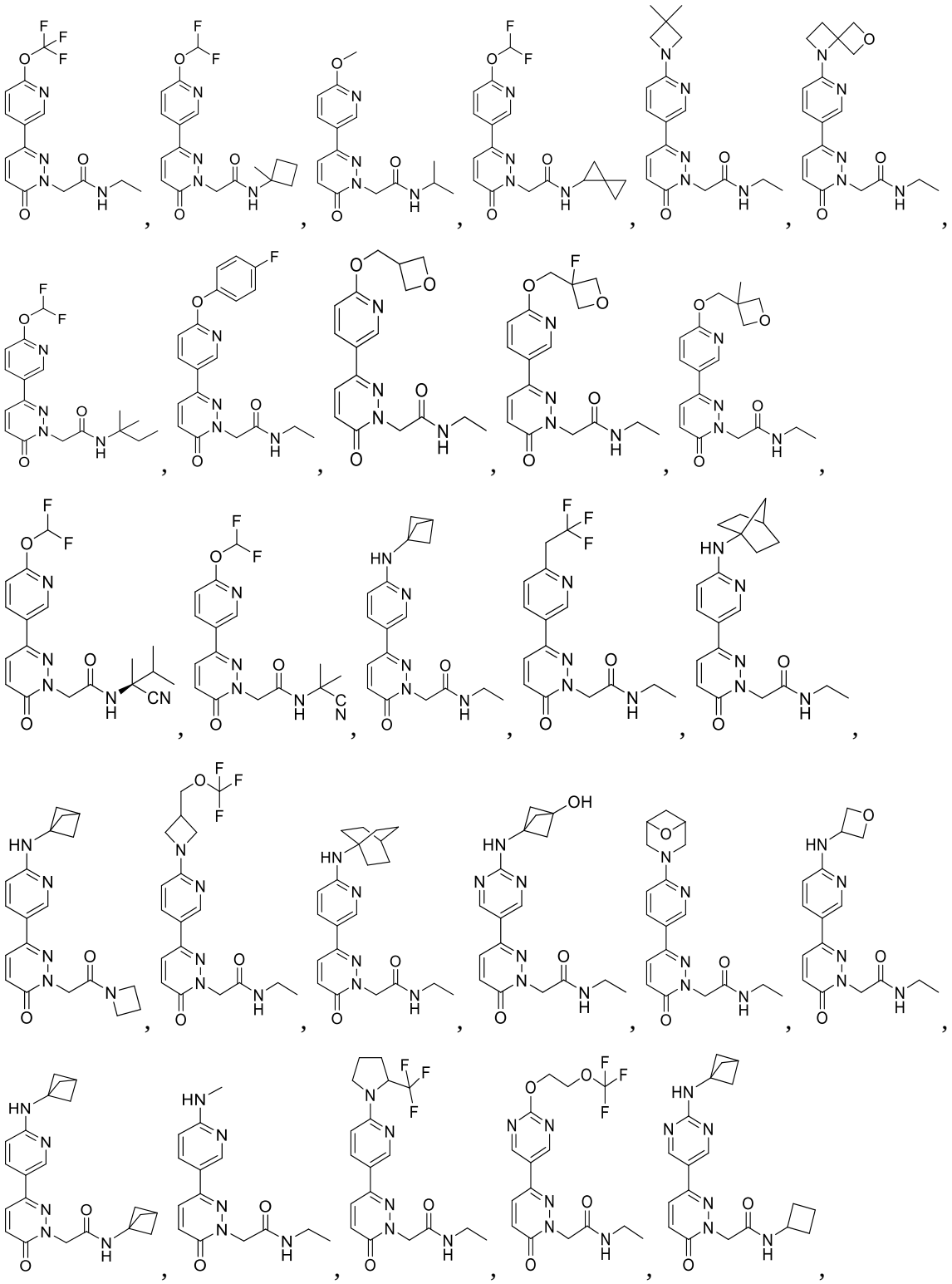






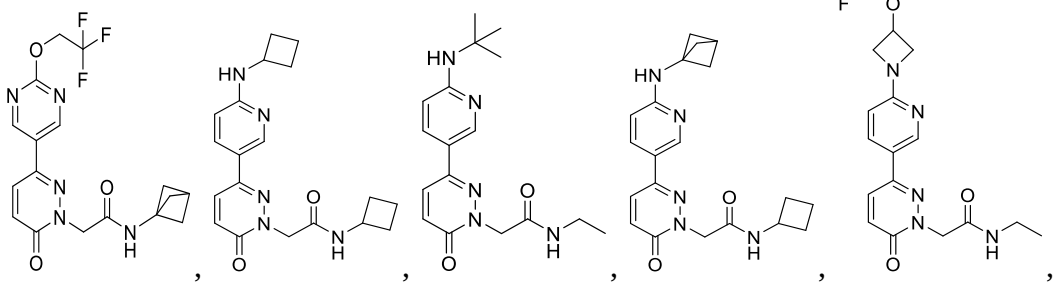
, , , , , , , and , or a salt of any one thereof.

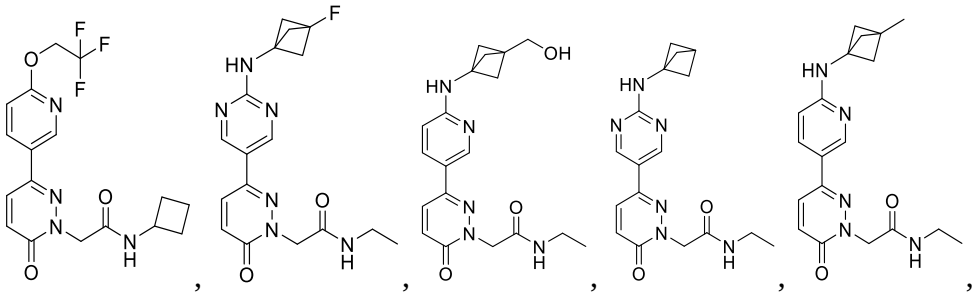
17. The compound of claim 1, selected from: , ,

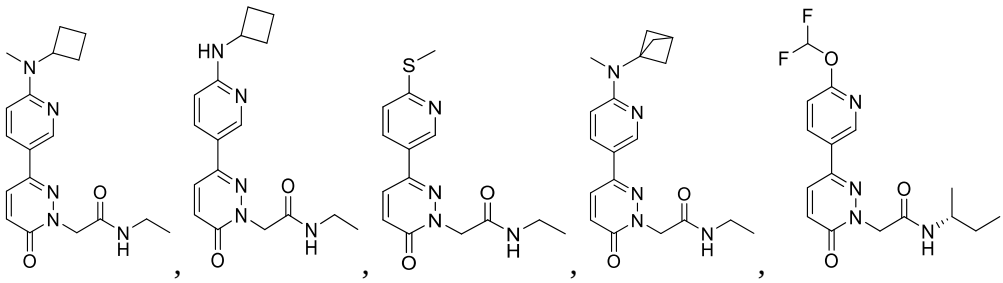
, , , , ,

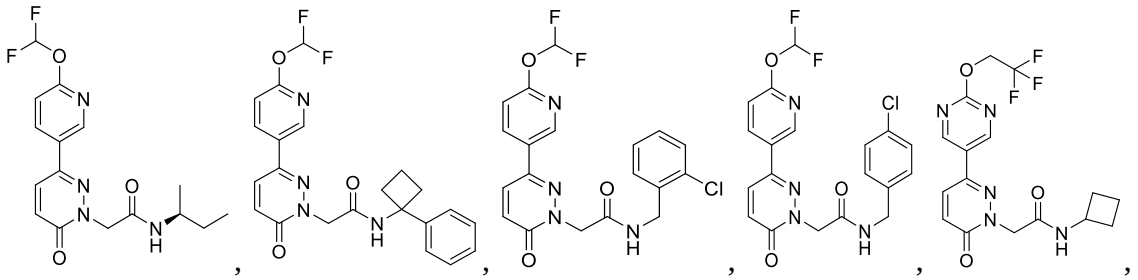
, , , , , ,

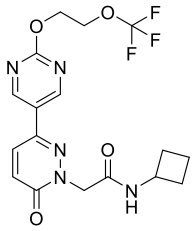
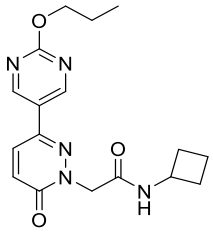
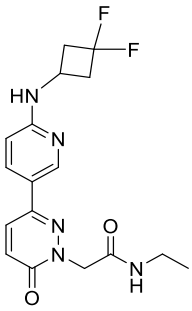
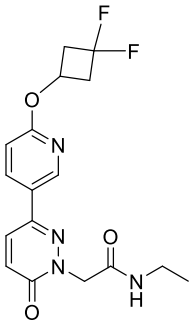
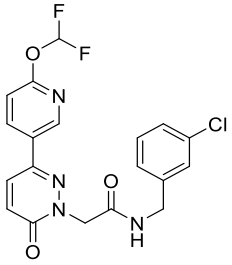
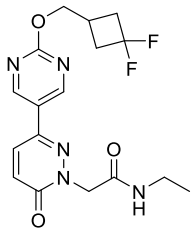
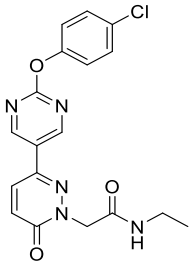


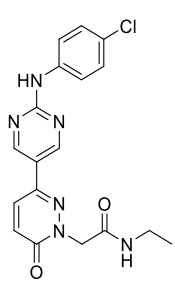
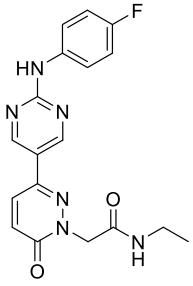
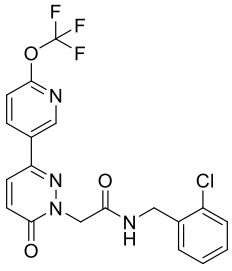
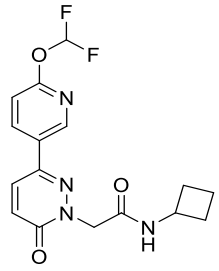
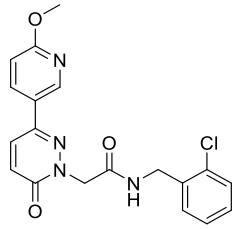
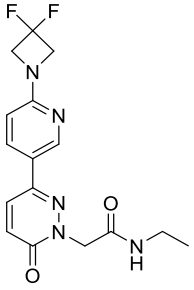
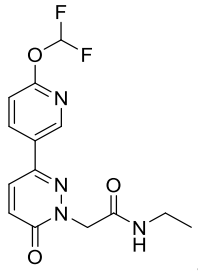
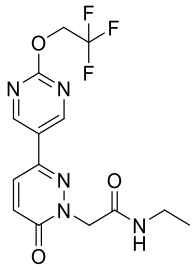
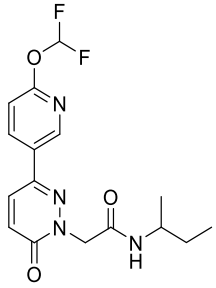
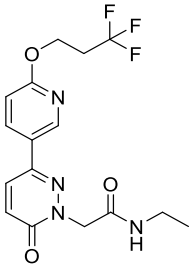
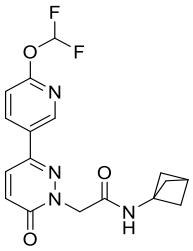
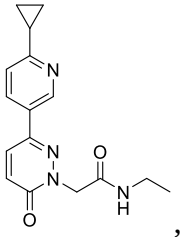


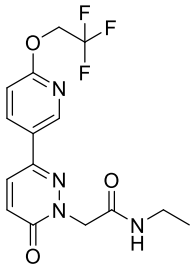
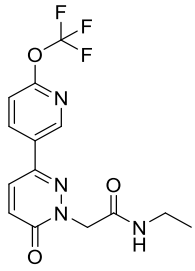
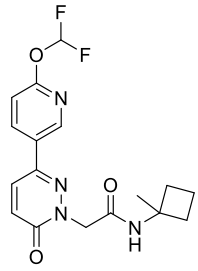
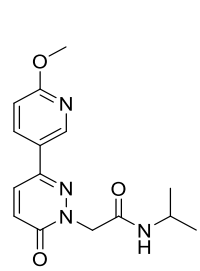
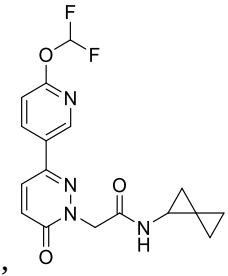
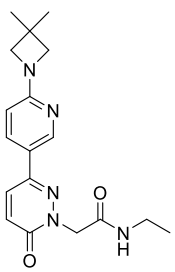
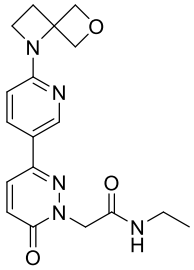
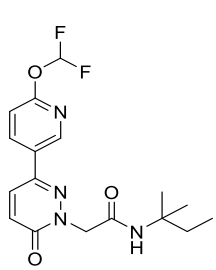
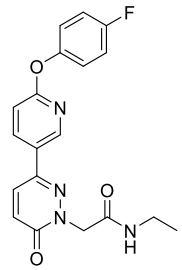
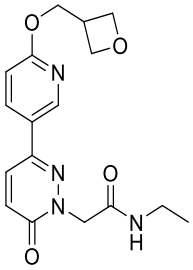
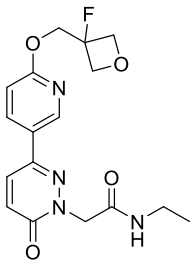
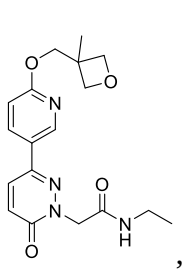
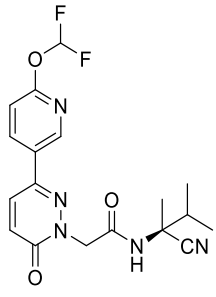
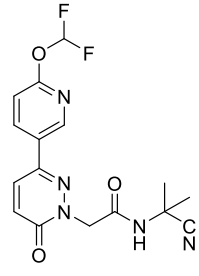
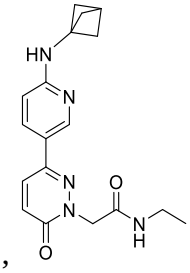
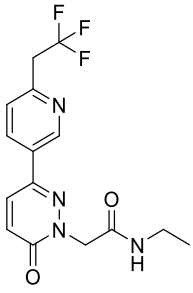
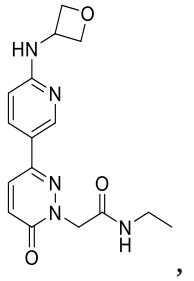
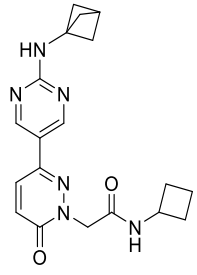
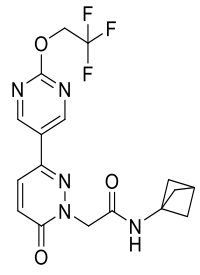
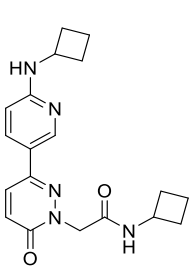
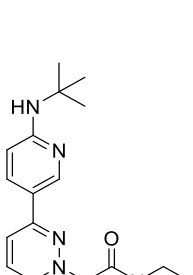
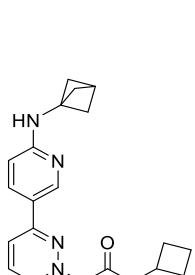
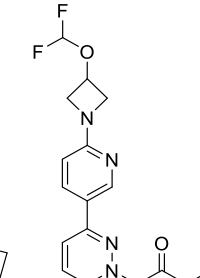
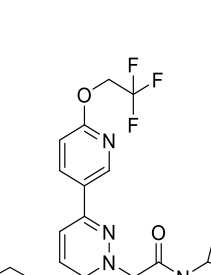
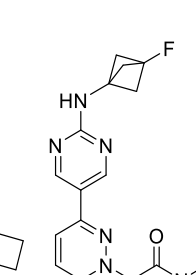






, , , , , , and , or a salt of any one thereof.

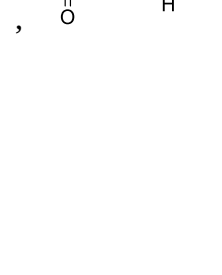
18. The compound of claim 1, selected from: , , , , , , , , , , , .

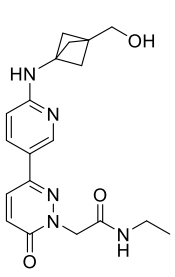
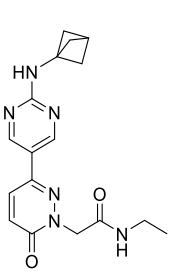
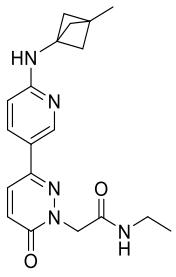
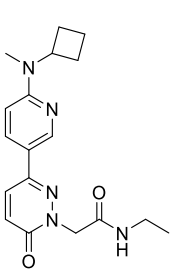
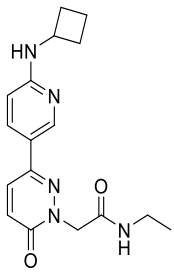
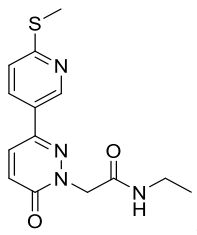

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

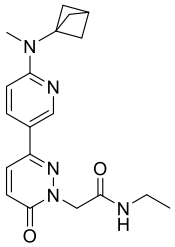
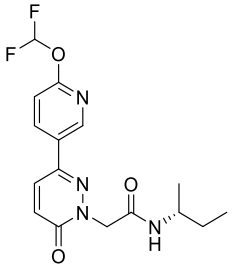
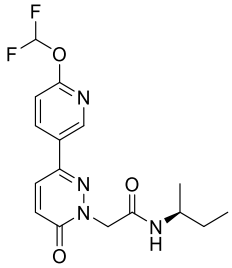
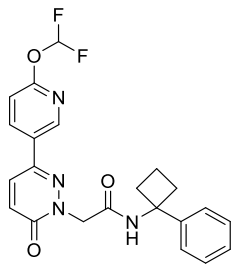
,

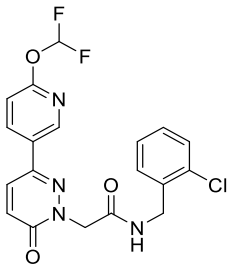
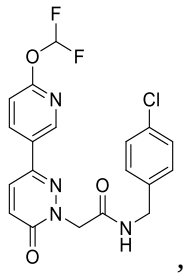
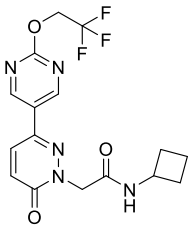
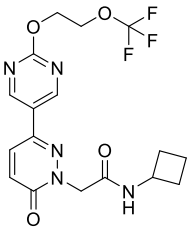
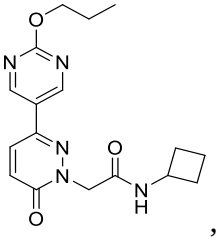
,

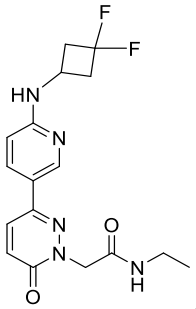
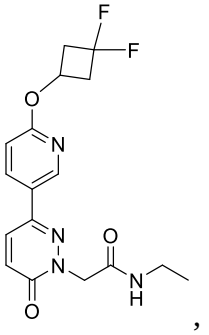
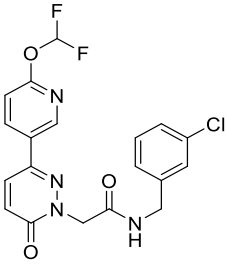
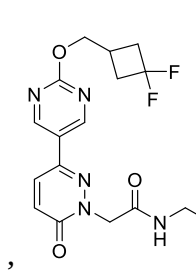
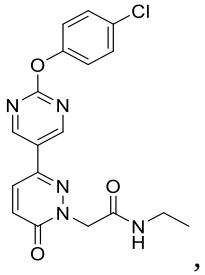
,

,

,

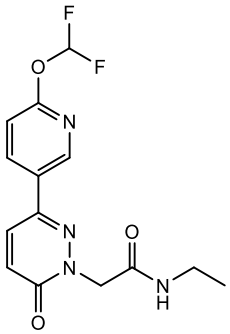
, , , , , ,

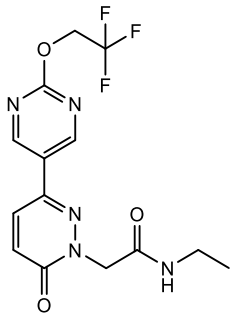
, , , ,

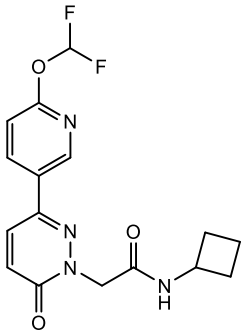
, , , , ,

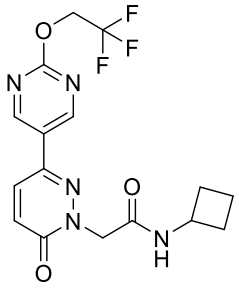
, , , , and ,

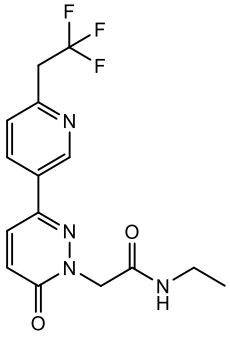
or a salt of any one thereof.

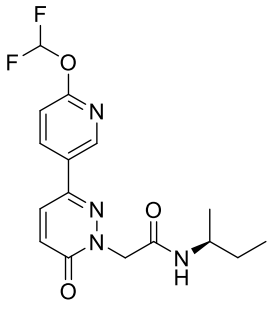
19. The compound of claim 1, selected from  or a salt thereof.

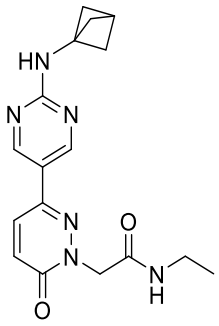
20. The compound of claim 1, selected from  or a salt thereof.

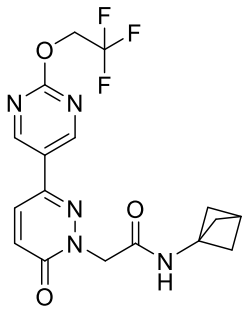
21. The compound of claim 1, selected from  or a salt thereof.

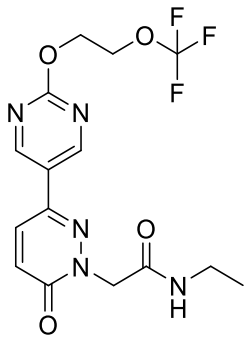
22. The compound of claim 1, selected from  or a salt thereof.

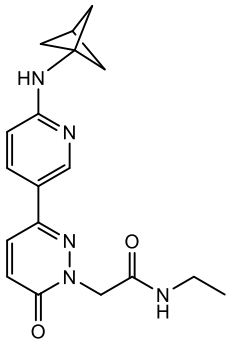
23. The compound of claim 1, selected from  or a salt thereof.

24. The compound of claim 1, selected from  or a salt thereof.

25. The compound of claim 1, selected from  or a salt thereof.

26. The compound of claim 1, selected from  or a salt thereof.

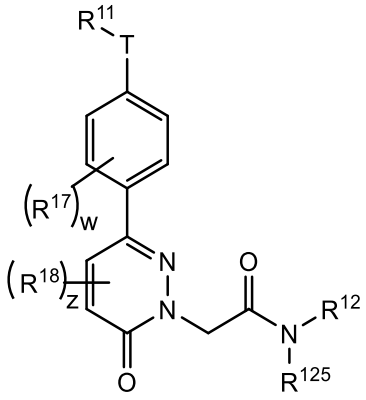
27. The compound of claim 1, selected from  or a salt thereof.

28. The compound of claim 1, selected from  or a salt thereof.

29. A pharmaceutical composition comprising a compound or salt of claim 1 and a pharmaceutically acceptable excipient.

30. Use of the pharmaceutical composition of claim 29 in the manufacture of a medicament for the treatment of neuromuscular condition.

31. A compound represented by Formula (II'):

 (II');

or a salt thereof, wherein:

T is selected from -O-, -NR^{14}-, -$CR^{15}R^{16}$-, -C(O)-, -S-, -S(O)-, and -$S(O)_2$;

R^{11} is selected from acetyl and C_{1-5} haloalkyl;

R^{125} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{125} together with R^{12} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^{12} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{10}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-OC(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-NO_2$, =O, =S, $=N(R^{20})$, and -CN; and

C_1 alkyl substituted with C_{3-10} carbocycle or 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{19}; and

C_{3-10} carbocycle, optionally substituted with one or more R^{19}; or

R^{12} together with R^{125} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^{14} is selected from:

hydrogen; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-NO_2$, and -CN;

R^{15} and R^{16} are each selected from:

hydrogen, halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-NO_2$, and -CN; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-NO_2$, and -CN;

R^{17} and R^{18} are each selected from:

halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, -CN, $-CHF_2$, $-CF_3$, and $-CH_2F$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-NO_2$, and -CN;

each R^{19} is independently selected from:

halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-OC(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-NO_2$, =O, =S, $=N(R^{20})$, and -CN; and

C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-OC(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-NO_2$, =O, =S, $=N(R^{20})$, and -CN; and

C_{3-10} carbocycle, optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-OC(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-NO_2$, =O, =S, $=N(R^{20})$, and –CN;

each R^{20} is independently selected from:

hydrogen; and

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

w is 0, 1, or 2; and

z is 0, 1, or 2.

32. The compound or salt of claim 31, wherein T is -O- or $-NR^{14}$-.

33. The compound or salt of claim 31, wherein R^{11} is selected from acetyl and C_{1-3} haloalkyl.

34. The compound or salt of claim 31, wherein R^{12} is selected from:

C_{1-4} alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, $-NH_2$, $-NO_2$, =O, =S, =NH, -CN; and

(C_{3-6} carbocycle)-CH_2-, and (5- to 6-membered heteroaryl)-CH_2-, wherein the C_{3-6} carbocycle, and 5- to 6-membered heteroaryl substituents are each optionally substituted with one or more R^{19}; and

C_{3-6} carbocycle, optionally substituted with one or more R^{19}; or

R^{12} together with R^{125} form a 4- to 6-membered ring, optionally substituted with one or more R^9.

35. The compound or salt of claim 31, wherein R^{12} is selected from:

C_{1-4} alkyl, and C_{1-4} haloalkyl; and

(C_{3-6} cycloalkyl)-CH_2-, (aryl)-CH_2-, and (6-membered heteroaryl)-CH_2-, wherein the C_{3-6} cycloalkyl, aryl, and 6-membered heteroaryl are each optionally substituted with one to three substituents independently selected from halo, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, C_{1-3} hydroxyalkyl, and =O; and

C_{4-6} cycloalkyl; or

R^{12} together with R^{125} form a 4- to 6-membered ring, optionally substituted with aryl.

36. The compound or salt of claim 31, wherein R^{12} is selected from:

C_{1-4} alkyl, optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, $-NH_2$, $-NO_2$, =O, =S, =NH, -CN; and

(C_{3-6} carbocycle)-CH_2-, and (5- to 6-membered heteroaryl)-CH_2-, wherein the C_{3-6} carbocycle, and 5- to 6-membered heteroaryl are each optionally substituted with one or more R^{19}; and

C_{3-6} carbocycle, optionally substituted with one or more R^{19}.

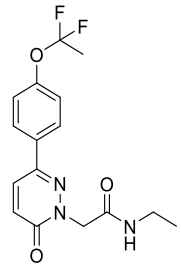
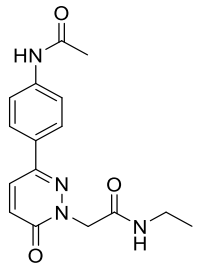
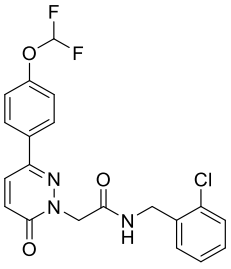
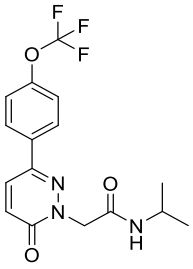
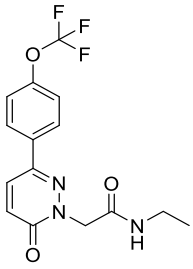
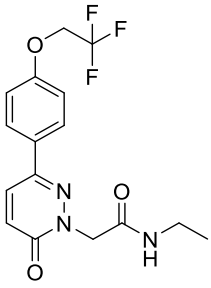
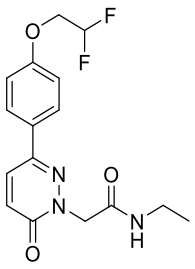
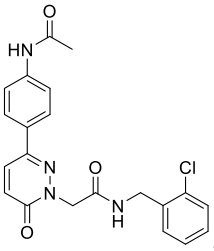
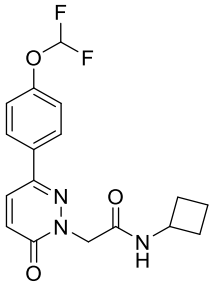
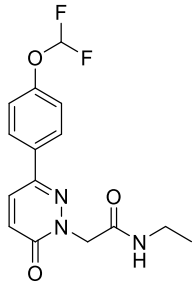
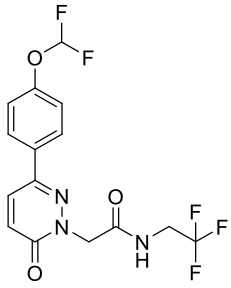
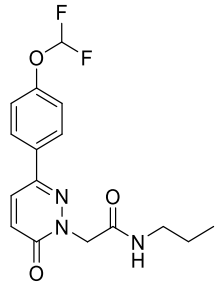
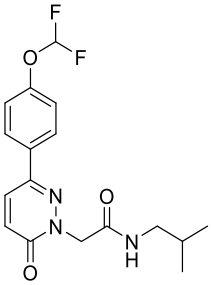
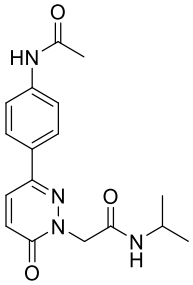
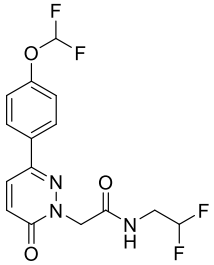
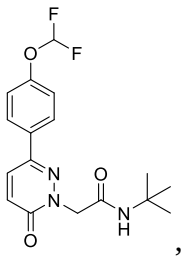
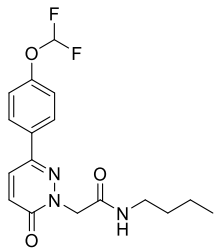
37. The compound or salt of claim 31, wherein R^{12} selected from:

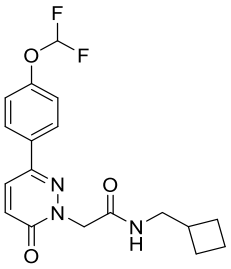
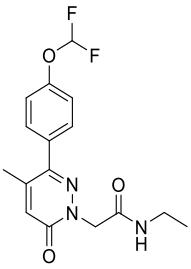
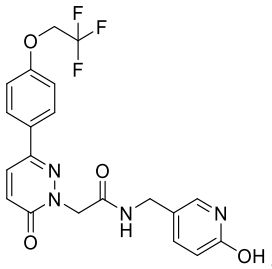
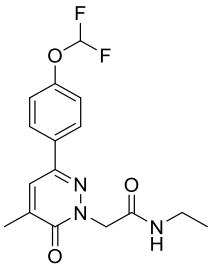
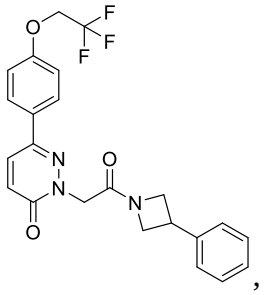
C_{1-4} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{10}$, $-N(R^{20})_2$, $-NO_2$, =O, =S, $=N(R^{20})$, -CN;

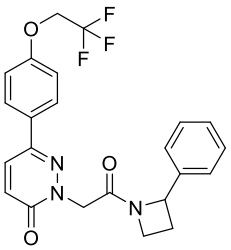
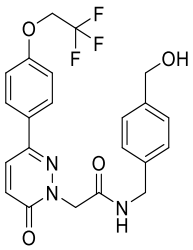
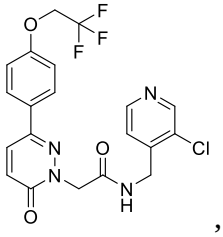
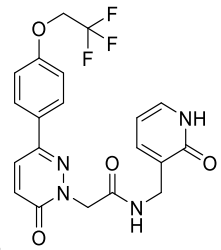
C_1 alkyl substituted with phenyl, heteroaryl and C_{3-6} cycloalkyl, wherein the phenyl, heteroaryl, and C_{3-6} cycloalkyl are each optionally substituted with one or more R^{19}; and

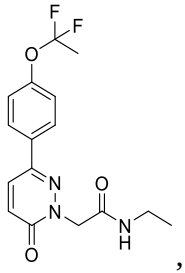
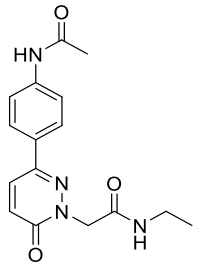
C_{3-6} cycloalkyl optionally substituted with one or more R^{19}.

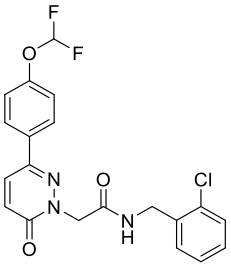
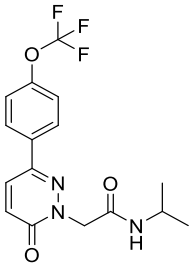
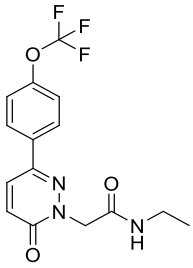
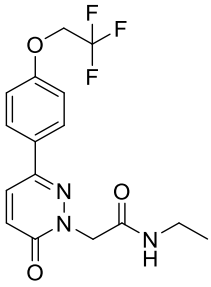
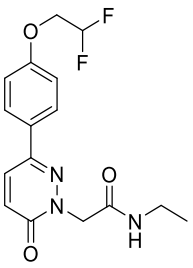
38. The compound or salt of claim 31, wherein w is 0 and z is 0.

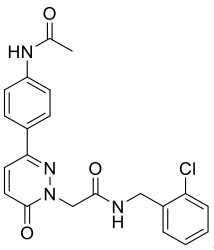
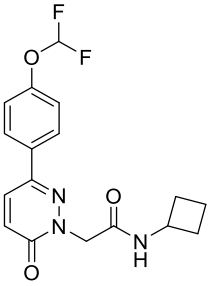
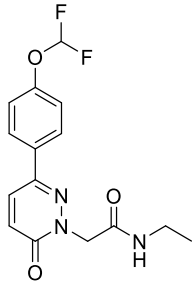
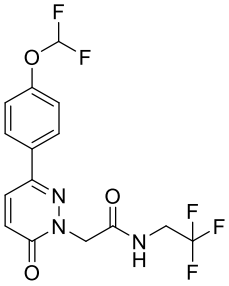
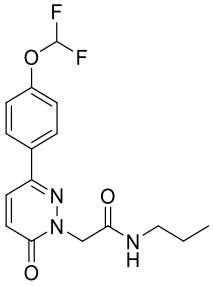
39. The compound or salt of claim 31, selected from: , , , , , , , , , , , , , , , , .

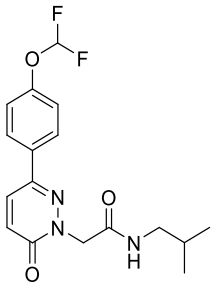
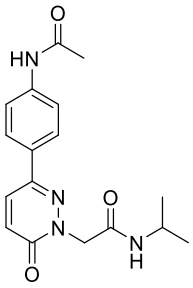
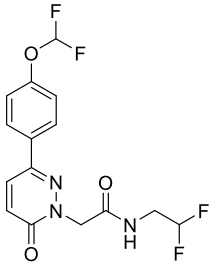
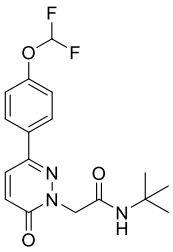
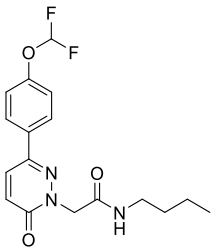
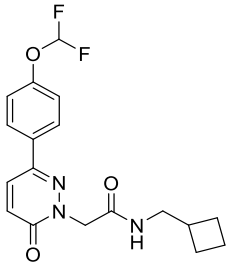
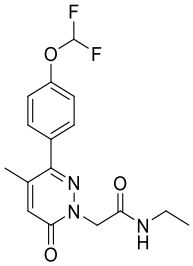
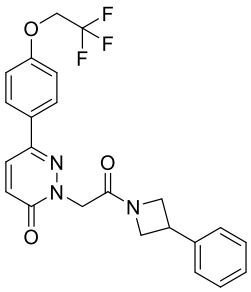
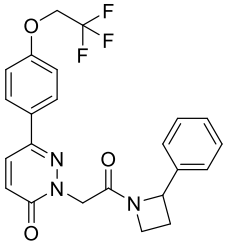
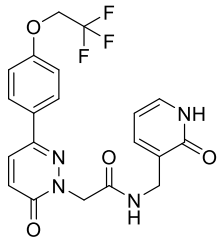
, , , , ,

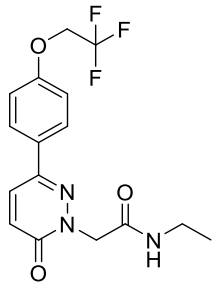
, , , , and a salt of any one thereof.

40. The compound or salt of claim 31, selected from: , ,

, , , , ,

, , , , ,

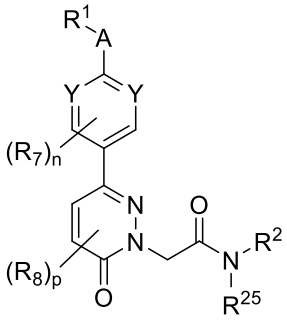
, , , , , , , , , , and a salt of any one thereof.

41. The compound or salt of claim 31, selected from .

42. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 41 and a pharmaceutically acceptable excipient.

43. Use of the pharmaceutical composition of claim 42 in the manufacture of a medicament for the treatment of neuromuscular condition.

44. Use of a compound or salt of any one of Formula (III'):

 (III');

or a salt thereof in the manufacture of a medicament for the treatment of activity-induced muscle damage, a neuromuscular condition, or a movement disorder,

wherein the neuromuscular condition is selected from Duchenne Muscular Dystrophy, Becker muscular dystrophy, myotonic dystrophy 1, myotonic dystrophy 2, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, limb girdle muscular dystrophy, tendinitis, and carpal tunnel syndrome;

wherein the movement disorder is selected from muscle spasticity associated with multiple sclerosis; Parkinson's disease; Alzheimer's disease; cerebral palsy; injury; and a traumatic event, wherein the traumatic event is selected from stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, and amyotrophic lateral sclerosis;

wherein:

each Y is independently selected from $C(R^3)$, N, and $N^+(-O^-)$;

A is absent or selected from -O-, $-NR^4-$, $-CR^5R^6-$, -C(O)-, -S-, -S(O)-, and $-S(O)_2-$;

R^1 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and

C_{2-6} alkynyl are each optionally substituted with one or more R^9; or

R^1 together with R^5 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted

with one or more R^9; or R^1 together with R^4 form a 3- to 10- membered heterocycle, wherein the 3- to 10- membered heterocycle is optionally substituted with one or more R^9; and

when A is absent, R^1 is additionally selected from H, and halogen;

R^{25} is selected from:

hydrogen, and C_{1-6} alkyl; or

R^{25} together with R^2 form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^2 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein the C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^9; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(O)N(R^{10})_2$, $-OC(O)N(R^{10})_2$, $-N(R^{10})C(O)OR^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-NO_2$, =O, =S, $=N(R^{10})$, –CN, C_{1-6} alkyl, and C_{3-10} carbocycle, wherein the C_{1-6} alkyl, and C_{3-10} carbocycle are optionally substituted with one or more substituents independently selected from halogen, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, and –CN; or

R^2 together with R^{25} form a 3- to 6-membered heterocycle, wherein the 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl,

-S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^3, R^5, and R^6 are each independently selected from:

hydrogen, halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, and -CN; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, and -CN; or

R^5 together with R^1 form a 3- to 10- membered heterocycle or C_{3-10} carbocycle, wherein the 3- to 10- membered heterocycle or C_{3-10} carbocycle is optionally substituted with one or more R^9;

R^4 is selected from:

hydrogen; and

C_{1-6} alkyl, optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, and -CN; or

R^4 together with R^1 form a 3- to 10-membered heterocycle, which is optionally substituted with one or more R^9;

R^7 and R^8 are each independently selected from:

halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -NO_2, and -CN;

each R^9 is independently selected from:

halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -C(O)N(R^{10})$_2$, -N(R^{10})C(O)R^{10}, -N(R^{10})C(O)N(R^{10})$_2$, -OC(O)N(R^{10})$_2$, -N(R^{10})C(O)OR^{10}, -C(O)OR^{10}, -OC(O)R^{10}, -S(O)R^{10}, -S(O)$_2$$R^{10}$, -$NO_2$, =O, =S, =N($R^{10}$), and -CN; and

C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -C(O)N(R^{10})$_2$, -N(R^{10})C(O)R^{10}, -N(R^{10})C(O)N(R^{10})$_2$, -OC(O)N(R^{10})$_2$, -N(R^{10})C(O)OR^{10}, -C(O)OR^{10}, -OC(O)R^{10}, -S(O)R^{10}, -S(O)$_2$$R^{10}$, -$NO_2$, =O, =S, =N($R^{10}$), and -CN;

each R^{10} is independently selected from:

hydrogen; and

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

n is 0, 1, or 2; and

p is 0, 1, or 2, and

wherein the medicament is to be administered to a subject in need thereof.

45. The use of claim 44, wherein the medicament is for the treatment of a neuromuscular condition.

46. The use of claim 45, wherein said neuromuscular condition is Duchenne Muscular Dystrophy.

47. The use of claim 44, wherein the medicament is for the treatment of a movement disorder.

48. The use of claim 47, wherein the medicament is for the treatment of activity-induced muscle damage.

49. The use of claim 48, wherein the compound or salt is to be administered in an amount sufficient to reduce involuntary muscle contractions.

50. The use of claim 49, wherein the compound or salt is to be administered in an amount sufficient to reduce involuntary muscle contractions by at least 10%.

51. The use of claim 44, wherein an additional therapeutic agent is to be further administered to the subject.

52. The use of claim 51, wherein the additional therapeutic agent is a corticosteroid.

53. The use of claim 52, wherein the corticosteroid is deflazacort or prednisone.

54. The use of claim 51, wherein the additional therapeutic agent is vamorolone.

55. The use of claim 51, wherein the additional therapeutic agent is a gene therapy.

56. The use of claim 55, wherein the gene therapy comprises the dystrophin gene or a variant or truncated version thereof.

57. The use of claim 55, wherein the gene therapy comprises microdystrophin.

58. The use of claim 51, wherein the additional therapeutic agent is eteplirsen.

59. The use of claim 51, wherein the additional therapeutic agent is ataluren.

60. The pharmaceutical composition of any one of claims 29 or 42 for use in therapy.