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(54) Title: PYRIDAZINONE COMPOUNDS FOR THE TREATMENT OF NEUROMUSCULAR DISEASES

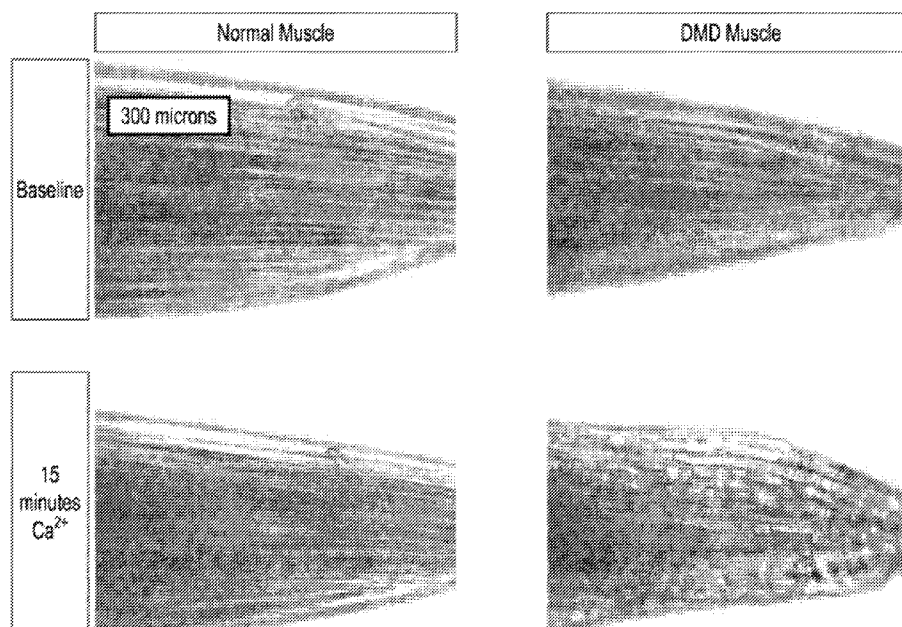


FIGURE 1

(57) **Abstract:** Substituted pyridazinone compounds, conjugates, and pharmaceutical compositions for use in the treatment of neuromuscular diseases, such as Duchenne Muscular Dystrophy (DMD), are disclosed herein. The disclosed compounds are useful, among other things, in the treating of DMD and modulating inflammatory inhibitors IL-1, IL-6 or TNF- α .

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CROSS-REFERENCE

[0001] This application claims the benefit of US Provisional Application Serial Number 63/024,439 filed May 13, 2020, 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 OF THE INVENTION

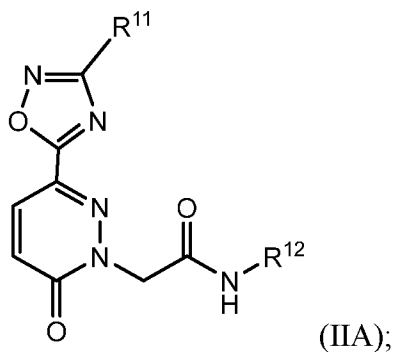
[0004] The present disclosure generally relates to substituted pyridazinone compounds or salts of Formula (IIA), (IIB), or (IIC) and pharmaceutical compositions thereof. The substituted pyridazinone compounds or salts of Formula (IIA), (IIB), or (IIC) disclosed herein may be used to treat or prevent neuromuscular diseases. In some embodiments, a compound or salt of Formula (IIA), (IIB), or (IIC) is an inhibitor of skeletal muscle contraction. In some embodiments, a compound or salt of Formula (IIA), (IIB), or (IIC) is an inhibitor of myosin. In some embodiments, a compound or salt of Formula (IIA), (IIB), or (IIC) is an inhibitor of skeletal muscle myosin II.

[0005] In some aspects, methods of treating a movement disorder may comprise administering a compound or salt of any one of Formula (I), (IIA), (IIB), or (IIC) to inhibit skeletal muscle myosin II. In some embodiments, said movement disorder comprises muscle spasticity. In some embodiments, said muscle spasticity may be selected from spasticity associated with multiple sclerosis, Parkinson's disease, Alzheimer's disease, or cerebral palsy, or injury, or a traumatic

event such as stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, or amyotrophic lateral sclerosis.

[0006] The disclosure provides compound and salts thereof for use in treating disease. In certain aspects, the disclosure provides a compound or salt of Formula (IIA), (IIB), or (IIC), pharmaceutical compositions thereof as well as methods of use in the treatment of disease.

[0007] In certain aspects, the disclosure provides a compound represented by Formula (IIA):



or a salt thereof, wherein:

R¹¹ is selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl are optionally substituted with one or more substituents independently selected from R¹⁷ and C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more substituents independently selected from R¹⁵;

R¹² is selected from: cyclobutyl optionally substituted with one or more substituents independently selected from R¹⁵; and ethyl optionally substituted with one or more substituents independently selected from R¹⁷;

each R¹⁵ is independently selected from:

halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN;

each R¹⁶ is independently selected from:

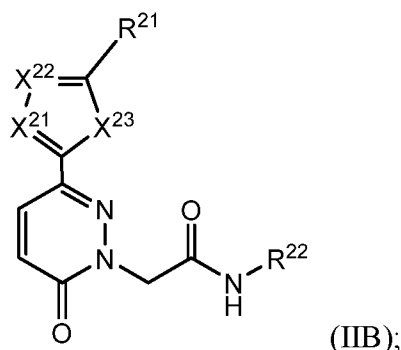
hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle;

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl; and

each R¹⁷ is independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN.

[0008] In certain aspects, the disclosure provides a compound represented by Formula (IIB):



or a salt thereof, wherein:

X^{21} and X^{22} are independently selected from N and C(R^{23}), wherein at least one of X^{21} and X^{22} is N;

X^{23} is selected from S and O;

R^{21} is selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, 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^{25} ; 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, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} ;

R^{22} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, C_{3-10} carbocycle and 3- to 10-membered heterocycle,

wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵;

R²³ is selected from:

hydrogen;

halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -NO₂ and -CN; and

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -NO₂, and -CN;

each R²⁵ is independently selected from:

halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), and -CN;

each R²⁶ is independently selected from:

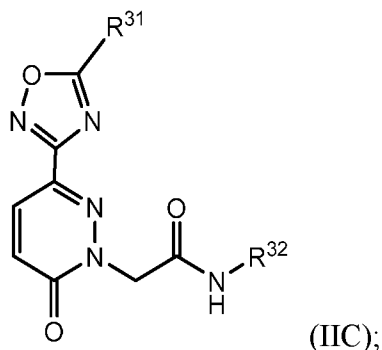
hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆

alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0009] In certain aspects, the disclosure provides a compound represented by Formula (IIC):



or a salt thereof, wherein:

R³¹ is selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵;

R³² is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle,

wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵; each R³⁵ is independently selected from:

halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), and -CN;

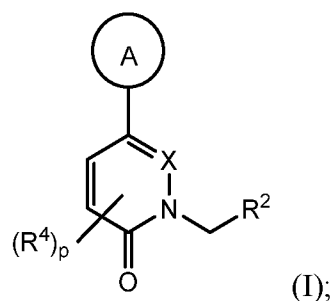
each R³⁶ is independently selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0010] In certain aspects, the disclosure provides a method of treating activity-induced muscle damage, comprising administering to a subject in need thereof a compound or salt of Formula (I):



or a salt thereof, wherein:

the A ring is selected from a 5-membered heteroaromatic ring optionally substituted by one or more substituents independently selected from R^1 ;

X is N or CH;

each R^1 is independently selected from:

halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, and $-CN$;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, 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^5 ; 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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ;

R^2 is selected from:

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

=N(R⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and -C(O)NR⁷R⁸;

each R⁴ is independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, -CN, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, and -CN;

each R⁵ is independently selected from:

halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN;

each R⁶ is independently selected from:

hydrogen; and

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

R⁷ is selected from hydrogen and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, and -CN;

R⁸ is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

p is 0, 1, or 2.

[0011] In certain aspects, the disclosure provides a method of treating a neuromuscular condition or treating activity-induced muscle damage or of inhibiting muscle myosin II, comprising administering to a subject in need thereof a compound or salt of any one of Formulas (I), (IIA), (IIB), or (IIC).

[0012] In certain aspects, the disclosure provides a method of treating a movement disorder, comprising administering to a subject in need thereof a compound or salt of any one of Formulas (I), (IIA), (IIB), or (IIC). In certain aspects, the disclosure provides a method of treating a disease disorder, comprising administering to a subject in need thereof a compound or salt of any one of Formulas (I), (IIA), (IIB), or (IIC), wherein the disease is selected from Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), myotonic dystrophy 1, myotonic dystrophy 2, facioscapulohumeral muscular dystrophy (FSHD), oculopharyngeal muscular dystrophy (OPMD), limb girdle muscular dystrophies (LGMD), tendinitis, carpal tunnel syndrome, Multiple sclerosis, Parkinson's disease, Alzheimer's disease, or cerebral palsy, or injury or a traumatic event such as stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, amyotrophic lateral sclerosis, Congenital muscular dystrophies (CMD), Emery-Dreifuss muscular dystrophy (EDMD), Facioscapulohumeral

muscular dystrophy (FSHD), Oculopharyngeal muscular dystrophy (OPMD), Congenital muscular dystrophies (CMD), Bethlem CMD, Fukuyama CMD, Muscle-eye-brain diseases (MEBs), Rigid spine syndromes, Ullrich CMD, Walker-Warburg syndromes (WWS), Congenital myopathies, distal myopathies, endocrine myopathies, inflammatory myopathies, metabolic myopathies, myofibrillar myopathies (MFM), scapuloperoneal myopathy, and cardiomyopathies.

[0013] In certain aspects, the disclosure provides a pharmaceutical composition comprising a compound or salt of any one Formulas (IIA), (IIB), or (IIC) or a pharmaceutically acceptable excipient.

INCORPORATION BY REFERENCE

[0014] 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

[0015] 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:

[0016] FIG.1 depicts excessive contraction-induced injuries, which precede the inflammation and irreversible fibrosis that characterizes late-stage DMD pathology; and

[0017] FIG.2 depicts 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.

[0018] FIG.3 depicts a comparison of creatine kinase, fast troponin, and slow troponin in healthy volunteers, patients with BMD, and patients with DMD.

[0019] FIG.4 depicts a comparison of creatine kinase, fast troponin, and slow troponin in patients with BMD and patients with DMD with respect to age.

[0020] FIG.5 depicts a comparison of creatine kinase, fast troponin, and slow troponin in patients with BMD and patients with DMD with respect to disease progression.

[0021] FIG. 6 depicts a comparison of creatine kinase, fast troponin, and myoglobin blood levels in subjects with BMD, LGMD, and McArdle’s pre and post exercise.

[0022] FIG. 7 depicts comparison of creatine kinase blood levels in subjects with BMD, LGMD, and McArdle’s pre and post exercise.

[0023] FIG. 8 depicts comparison of myoglobin blood levels in subjects with BMD, LGMD, and McArdle's pre and post exercise.

DETAILED DESCRIPTION OF THE INVENTION

[0024] 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 methods and structures within the scope of these claims and their equivalents be covered thereby.

[0025] In certain aspects, the disclosure provides methods for treating neuromuscular conditions through selective inhibition of fast-fiber skeletal muscle myosin. In particular, methods of the disclosure may be used in the treatment of DMD and other neuromuscular conditions.

[0026] Skeletal muscle is mainly composed of two types of fibers, slow-twitch muscle fiber (i.e., type I) and fast-twitch muscle fiber (i.e., type II). In each muscle, the two types of fibers are configured in a mosaic-like arrangement, with differences in fiber type composition in different muscles and at different points in growth and development. Slow-twitch muscle fibers have excellent aerobic energy production ability. Contraction rate of the slow-twitch muscle fiber is low but tolerance to fatigue is high. Slow-twitch muscle fibers typically have a higher concentration of mitochondria and myoglobin than do fast-twitch fibers and are surrounded by more capillaries than are fast-twitch fibers. Slow-twitch fibers contract at a slower rate due to lower myosin ATPase activity and produce less power compared to fast-twitch fibers, but they are able to maintain contractile function over longer-terms, such as in stabilization, postural control, and endurance exercises.

[0027] Fast twitch muscle fibers in humans are further divided into two main fiber types depending on the specific fast skeletal myosin they express (Type IIA, IIX/d). A third type of fast fiber (Type IIB) exists in other mammals but is rarely identified in human muscle. Fast-twitch muscle fibers have excellent anaerobic energy production ability and are able to generate high amounts of tension over a short period of time. Typically, fast-twitch muscle fibers have lower concentrations of mitochondria, myoglobin, and capillaries compared to slow-twitch fibers, and thus can fatigue more quickly. Fast-twitch muscles produce quicker force required for power and resistance activities.

[0028] The proportion of the type I and type II can vary in different individuals. For example, non-athletic individuals can have close to 50% of each muscle fiber types. Power athletes can

have a higher ratio of fast-twitch fibers, e.g., 70-75% type II in sprinters. Endurance athletes can have a higher ratio of slow-twitch fibers, e.g., 70-80% in distance runners. The proportion of the type I and type II fibers can also vary depending on the age of an individual. The proportion of type II fibers, especially the type IIX, can decline as an individual ages, resulting in a loss in lean muscle mass.

[0029] The contractile action of skeletal muscle leads to muscle damage in subjects with neuromuscular disease, e.g., DMD, and this damage appears to be more prevalent in fast fibers. It has been observed that acute force drop after lengthening injury is greater in predominantly fast type II fiber muscles compared to predominantly slow type I fiber muscles in dystrophy mouse models. It has also been demonstrated that the degree of acute force drop and histological damage in dystrophy mouse models is proportional to peak force development during lengthening injury. Excessive contraction-induced injuries, which precede the inflammation and irreversible fibrosis that characterizes late-stage DMD pathology are shown in FIG. 1 [Figure adapted: Claflin and Brooks, Am J Brooks, Physiol Cell, 2008,]. Contraction-induced muscle damage in these patients may be reduced by limiting peak force generation in type II fibers and possibly increasing reliance on healthier type I fibers. 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 as shown in FIG. 2. [Source: Li and Arner, PLoS ONE, 2015].

[0030] Inhibitors of skeletal muscle myosin that are not selective for the type II fibers may lead to excessive inhibition of skeletal muscle contraction including respiratory function and unwanted inhibition of cardiac activity as the heart shares several structural components (such as type I myosin) with type I skeletal muscle fibers. While not wishing to be bound by a particular mechanistic theory, this disclosure provides selective inhibitors of fast-fiber skeletal muscle myosin as a treatment option for Becker muscular dystrophy (BMD), Duchenne muscular dystrophy (DMD), Limb-girdle muscular dystrophies (LGMD), McArdle disease, and other neuromuscular conditions. The targeted inhibition of type II skeletal muscle myosin may reduce skeletal muscle contractions while minimizing the impact on a subject's daily activities.

[0031] When healthy muscle is subjected to excessive, unaccustomed exercise, it develops soreness and sustained reductions in strength and range of motion. Proteins also leak from injured muscle fibers into circulation, including creatine kinase (CK), lactate dehydrogenase and myoglobin. These biomarkers are not unique to either fast or slow fibers and so do not provide detail regarding differences in fiber responses to injury. Troponin I (TNNI) is a component of the troponin complex that controls initiation of contraction of muscle by calcium. It is distinct in that

there is a different isoform for each type of striated muscle: TNNI1 in slow skeletal muscle, TNNI2 in fast skeletal muscle and TNNI3 in cardiac muscle. Selective enzyme-linked immunosorbent assays (ELISAs) have been used to demonstrate that TNNI2 but not TNNI1 is elevated in circulation after injurious exercise, even under extreme conditions.

[0032] DMD and BMD are caused by an absence (DMD) or truncation (BMD) of the dystrophin proteins. Dystrophin provides a structural link between the actin cytoskeleton and the basement membrane through the dystrophin-glycoprotein complex. When dystrophin is absent or truncated, contraction of muscle leads to heightened muscle stress and injury with normal use. While the sensitivity to injury is much higher in DMD muscle than in BMD or healthy muscle, fast fibers still appear to be more susceptible than slow fibers, with young DMD patients exhibiting histological evidence of disruption in fast fibers⁷ and early loss of type IIX fibers. Example 10 shows the relative susceptibility of these fibers to leak muscle contents, such as troponin, creatine kinase, or myoglobin. In some embodiments, this disclosure provides selective inhibitors of fast-fiber skeletal muscle myosin as a treatment option for DMD, BMD, McArdle's disease, or Limb-girdle muscular dystrophies.

Definitions

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0034] As used in the specification and claims, the singular form “a”, “an” and “the” includes plural references unless the context clearly dictates otherwise.

[0035] The term “C_{x-y}” or “C_x-C_y” when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the term “C₁₋₆alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons.

[0036] The terms “C_{x-y}alkenyl” and “C_{x-y}alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

[0037] The term “carbocycle” as used herein refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is carbon. Carbocycle includes 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene.

A bicyclic carbocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. A bicyclic carbocycle further includes spiro bicyclic rings such as spiropentane. A bicyclic carbocycle includes any combination of ring sizes such as 3-3 spiro ring systems, 4-4 spiro ring systems, 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, naphthyl, and bicyclo[1.1.1]pentanyl.

[0038] The term “aryl” refers to an aromatic monocyclic or aromatic polycyclic hydrocarbon ring system. The aromatic monocyclic or aromatic polycyclic hydrocarbon ring system contains only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, i.e., it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene.

[0039] The term “cycloalkyl” refers to a saturated ring in which each atom of the ring is carbon. Cycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyls include, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, spiropentane, norbornyl (i.e., bicyclo[2.2.1]heptanyl), decalinyl, 7,7 dimethyl bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and the like.

[0040] The term “cycloalkenyl” refers to an unsaturated ring in which each atom of the ring is carbon and there is at least one double bond between two ring carbons. Cycloalkenyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, e.g., cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[0041] The term “halo” or, alternatively, “halogen” or “halide,” means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[0042] The term “haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl,

2,2,2-trifluoroethyl, 1-chloromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the haloalkyl radical is optionally further substituted as described herein.

[0043] The term “heterocycle” as used herein refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. A bicyclic heterocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. A bicyclic heterocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. A bicyclic heterocycle further includes spiro bicyclic rings, e.g., 5 to 12-membered spiro bicycles, such as 2-oxa-6-azaspiro[3.3]heptane.

[0044] The term "heteroaryl" refers to a radical derived from a 5 to 18 membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is aromatic, i.e., it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl,

isoquinolyl, indoliziny, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazoliny, naphthyridiny, 1,6-naphthyridinony, oxadiazolyl, 2-oxoazepiny, oxazolyl, oxirany, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazoliny, 1-phenyl-1*H*-pyrroly, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pteridiny, puriny, pyrroly, pyrazolyl, pyrazolo[3,4-d]pyrimidiny, pyridiny, pyrido[3,2-d]pyrimidiny, pyrido[3,4-d]pyrimidiny, pyraziny, pyrimidiny, pyridaziny, pyrroly, quinazoliny, quinoxaliny, quinoliny, isoquinoliny, tetrahydroquinoliny, 5,6,7,8-tetrahydroquinazoliny, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidiny, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-d]pyrimidiny, 5,6,7,8-tetrahydropyrido[4,5-c]pyridaziny, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triaziny, thieno[2,3-d]pyrimidiny, thieno[3,2-d]pyrimidiny, thieno[2,3-c]pyridiny, and thiophenyl (*i.e.* thienyl).

[0045] The term "heterocycloalkyl" refers to a saturated ring with carbon atoms and at least one heteroatom. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. The heteroatoms in the heterocycloalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl is attached to the rest of the molecule through any atom of the heterocycloalkyl, valence permitting, such as any carbon or nitrogen atoms of the heterocycloalkyl. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolany, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, oxazolidiny, piperidiny, piperaziny, 4-piperidony, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyrany, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, 2-oxa-6-azaspiro[3.3]heptane, and 1,1-dioxo-thiomorpholiny.

[0046] The term "heterocycloalkenyl" refers to an unsaturated ring with carbon atoms and at least one heteroatom and there is at least one double bond between two ring carbons. Heterocycloalkenyl does not include heteroaryl rings. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkenyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a heterocycloalkenyl comprises five to seven ring atoms. The heterocycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, *e.g.*, pyrroline (dihydropyrrole), pyrazoline

(dihydropyrazole), imidazoline (dihydroimidazole), triazoline (dihydrotriazole), dihydrofuran, dihydrothiophene, oxazoline (dihydrooxazole), isoxazoline (dihydroisoxazole), thiazoline (dihydrothiazole), isothiazoline (dihydroisothiazole), oxadiazoline (dihydrooxadiazole), thiadiazoline (dihydrothiadiazole), dihydropyridine, tetrahydropyridine, dihydropyridazine, tetrahydropyridazine, dihydropyrimidine, tetrahydropyrimidine, dihydropyrazine, tetrahydropyrazine, pyran, dihydropyran, thiopyran, dihydrothiopyran, dioxine, dihydrodioxine, oxazine, dihydrooxazine, thiazine, and dihydrothiazine.

[0047] The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., an NH or NH₂ of a compound. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds.

[0048] In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro (-NO₂), imino (=N-H), oximo (=N-OH), hydrazino (=N-NH₂), -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro (-NO₂), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH₂), -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2) and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2); wherein each R^a is

independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each R^a , valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo ($=O$), thioxo ($=S$), cyano ($-CN$), nitro ($-NO_2$), imino ($=N-H$), oximo ($=N-OH$), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[0049] Double bonds to oxygen atoms, such as oxo groups, are represented herein as both “ $=O$ ” and “ (O) ”. Double bonds to nitrogen atoms are represented as both “ $=NR$ ” and “ (NR) ”. Double bonds to sulfur atoms are represented as both “ $=S$ ” and “ (S) ”.

[0050] The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0051] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0052] The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as

peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0053] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

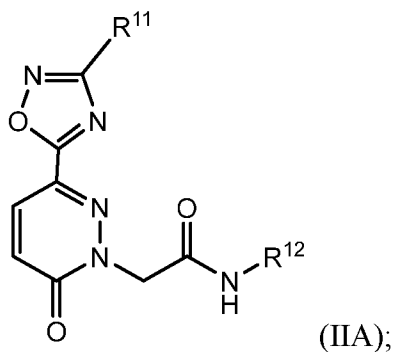
[0054] As used herein, “treatment” or “treating” refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition including but not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit can include, for example, the eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit can include, for example, the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may

not have been made. Treatment via administration of a compound described herein does not require the involvement of a medical professional.

Compounds

[0055] The following is a discussion of compounds and salts thereof that may be used in the methods of the disclosure. In certain embodiments, the compounds and salts are described in Formulas (IIA), (IIB), or (IIC).

[0056] In one aspect, disclosed herein is a compound represented by Formula (IIA):



or a salt thereof, wherein:

R^{11} is selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, $-CN$, 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^{15} ; 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, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl are optionally substituted with one or more substituents independently selected from R^{17} and C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more substituents independently selected from R^{15} ;

R¹² is selected from: cyclobutyl optionally substituted with one or more substituents independently selected from R¹⁵; and ethyl optionally substituted with one or more substituents independently selected from R¹⁷;

each R¹⁵ is independently selected from:

halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN;

each R¹⁶ is independently selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle;

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl; and

each R¹⁷ is independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN.

[0057] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from:

hydrogen;

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from R¹⁷ and C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more substituents independently selected from R¹⁵.

[0058] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵.

[0059] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is a C₃₋₁₀ carbocycle optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵.

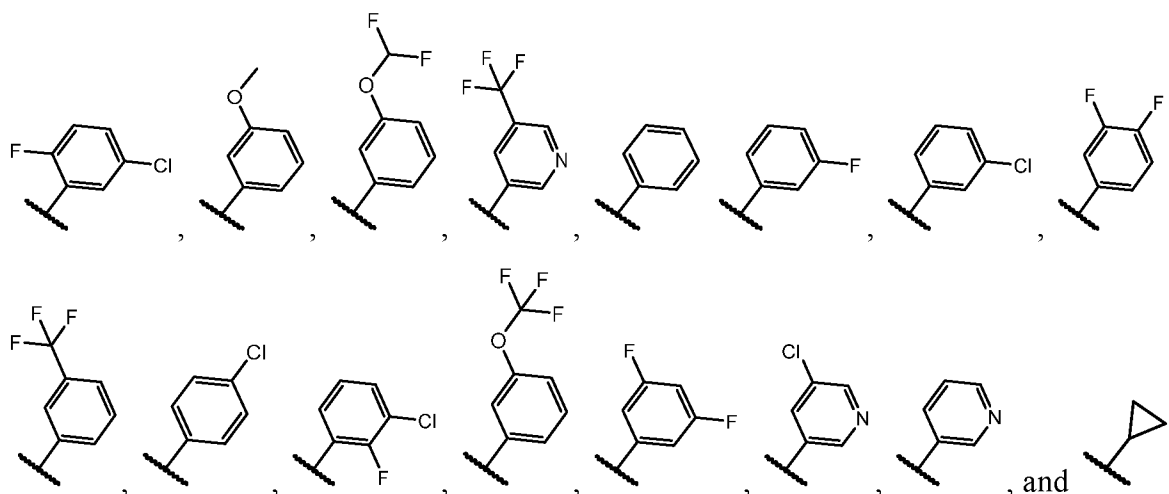
[0060] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is a 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵.

[0061] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from cycloalkyl, aryl and heteroaryl, each of which is optionally substituted with one or more substituents independently selected from R¹⁵.

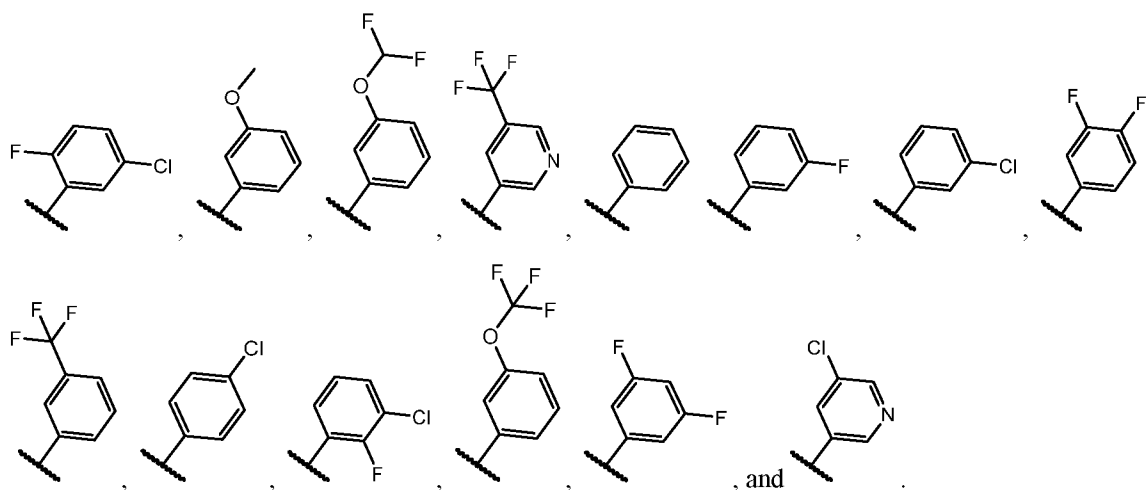
[0062] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from phenyl, pyridyl, and cyclopropyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, and C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen.

[0063] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from phenyl, 3-pyridyl, and cyclopropyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OMe, -OCF₃, -OCHF₂, and -CF₃.

[0064] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from



[0065] In certain embodiments, for a compound or salt of Formula (IIA), R¹¹ is selected from



[0066] In certain embodiments, for a compound or salt of Formula (IIA), R¹² is cyclobutyl optionally substituted with one or more substituents independently selected from:

halogen, $-\text{OR}^{16}$, $-\text{N}(\text{R}^{16})_2$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{N}(\text{R}^{16})_2$, $-\text{N}(\text{R}^{16})\text{C}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{OR}^{16}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{NO}_2$, and $-\text{CN}$; and

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -NO₂, and -CN.

[0067] In certain embodiments, for a compound or salt of Formula (IIA), R¹² is ethyl optionally substituted with halogen, -OR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -NO₂, and -CN.

[0068] In certain embodiments, for a compound or salt of Formula (IIA), R¹² is selected from ethyl and cyclobutyl.

[0069] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁵ is selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN.

[0070] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁵ is selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -C(O)N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁶, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)N(R¹⁶)₂, -N(R¹⁶)C(O)OR¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -NO₂, =O, =S, =N(R¹⁶), and -CN.

[0071] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁵ is selected from: halogen, -OR¹⁶, -N(R¹⁶)₂, =O, -CN, and C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -N(R¹⁶)₂, -NO₂, =O, and -CN;

[0072] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is hydrogen.

[0073] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[0074] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[0075] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is selected from C₃₋₁₀ 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, -NO₂, -NH₂,

=O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

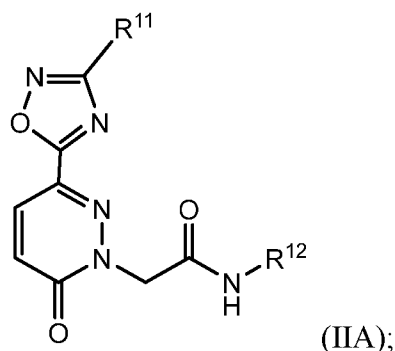
[0076] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is a C₃₋₁₀ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl.

[0077] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁶ is a 3- to 10-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl.

[0078] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁷ is selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -NO₂, =O, =S, and -CN.

[0079] In certain embodiments, for a compound or salt of Formula (IIA), R¹⁷ is halogen.

[0080] In one aspect, disclosed herein is a compound represented by Formula (IIA):



or a salt thereof, wherein:

R¹¹ is selected from:

hydrogen;

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, -N(R¹⁶)₂, -C(O)R¹⁶, -NO₂, =O, =S, =N(R¹⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵;

R^{12} is selected from cyclobutyl optionally substituted with one or more substituents independently selected from R^{15} ; and ethyl optionally substituted with one or more substituents independently selected from R^{17} ;

each R^{15} is independently selected from:

halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, 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, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, and $-CN$;

each R^{16} is independently selected from:

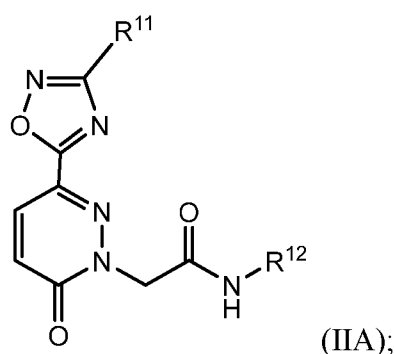
hydrogen;

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

C_{3-3} carbocycle, and 5- to 9-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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl; and

each R^{17} is independently selected from halogen, $-OH$, $-OMe$, $-SH$, $-NH_2$, $-NO_2$, $=O$, $=S$, and $-CN$.

[0081] In one aspect, disclosed herein is a compound represented by Formula (IIA):



or a salt thereof, wherein:

R^{11} is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-CN$, 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^{15} ; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -NO₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R¹⁵;

R¹² is selected from cyclobutyl and ethyl;

each R¹⁵ is independently selected from:

halogen, -OR¹⁶, and -CN; and

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR¹⁶, -SR¹⁶, and -CN; and

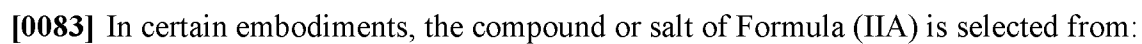
each R¹⁶ is independently selected from:

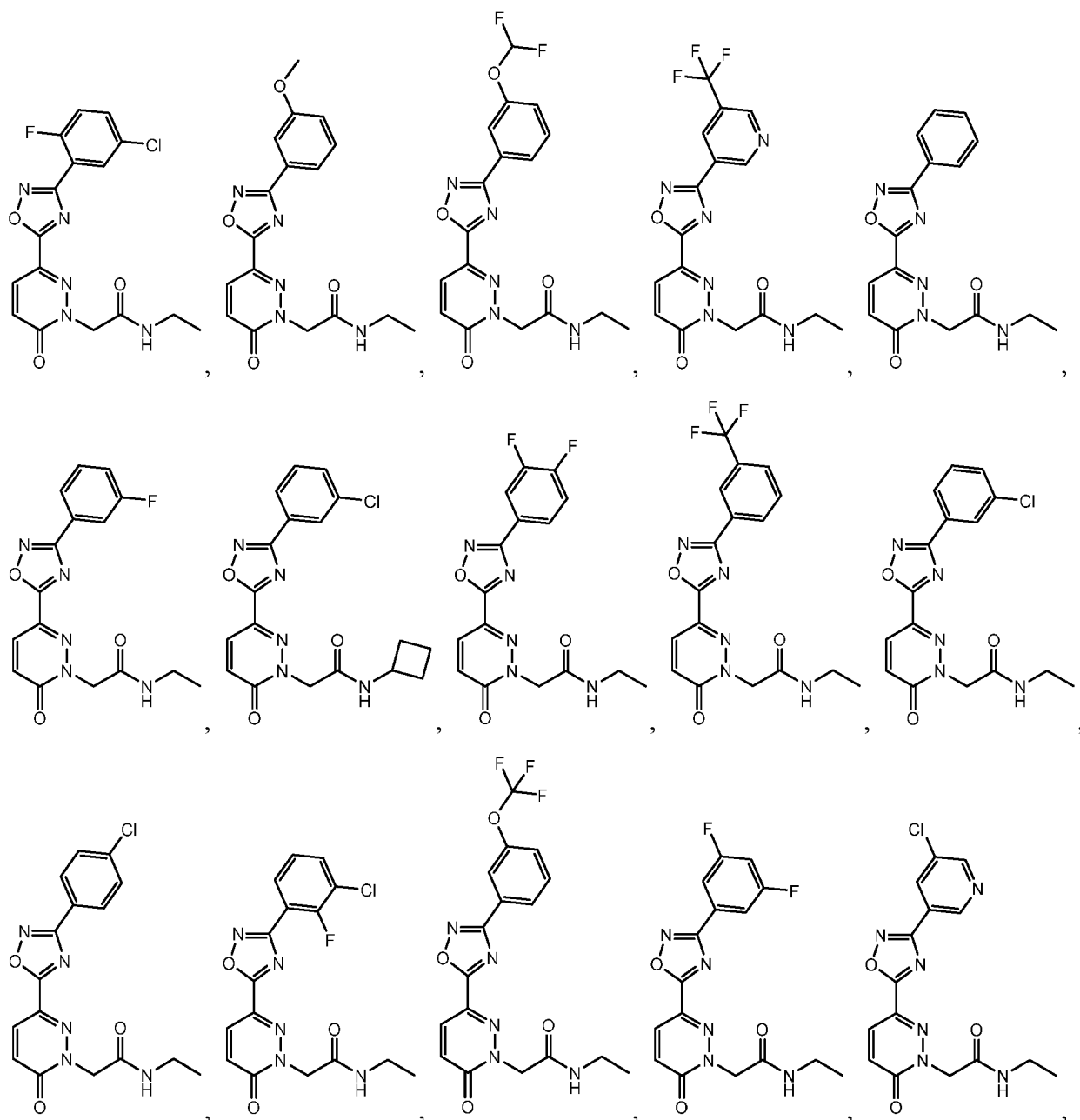
hydrogen;

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₆ carbocycle, and 5- to 9-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

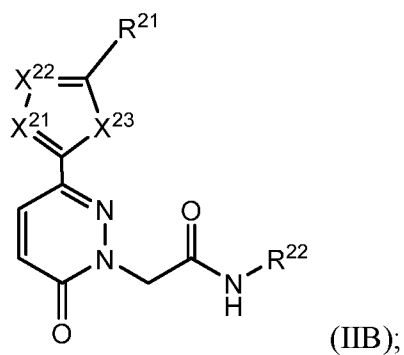
[0082] In certain embodiments, the compound or salt of Formula (IIA) is selected from:





and a salt of any one thereof.

[0084] In one aspect, disclosed herein is a compound represented by Formula (IIB):



or a salt thereof, wherein:

X²¹ and X²² are independently selected from N and C(R²³), wherein at least one of X²¹ and X²² is N;

X²³ is selected from S and O;

R²¹ is selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵;

R²² is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3-

to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵;

R²³ is selected from:

hydrogen;

halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -NO₂ and -CN; and

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -NO₂, and -CN;

each R²⁵ is independently selected from:

halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), and -CN;

each R²⁶ is independently selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0085] In certain embodiments, for a compound or salt of Formula (IIB), X²³ is O. In certain embodiments, X²³ is S. In certain embodiments, for a compound or salt of Formula (IIB), X²¹ is N and X²² is CR²³. In certain embodiments, for a compound or salt of Formula (IIB), X²² is N and X²¹ is CR²³. In certain embodiments, for a compound or salt of Formula (IIB), X²² is N and X²¹ is N. In certain embodiments, for a compound or salt of Formula (IIB), X²³ is O, X²¹ is N

and X^{22} is N. In certain embodiments, for a compound or salt of Formula (IIB), X^{23} is O, X^{21} is CR^{23} and X^{22} is N. In certain embodiments, for a compound or salt of Formula (IIB), X^{23} is O, X^{21} is N and X^{22} is CR^{23} . In certain embodiments, for a compound or salt of Formula (IIB), X^{23} is S, X^{21} is N and X^{22} is N. In certain embodiments, for a compound or salt of Formula (IIB), X^{23} is S, X^{21} is CR^{23} and X^{22} is N. In certain embodiments, for a compound or salt of Formula (IIB), X^{23} is S, X^{21} is N and X^{22} is CR^{23} .

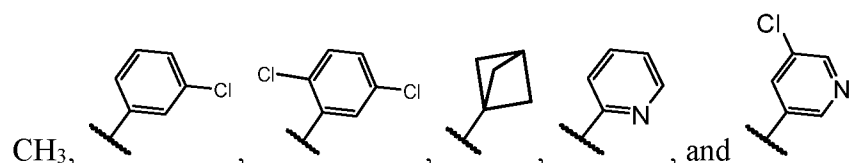
[0086] In certain embodiments, for a compound or salt of Formula (IIB), R^{21} is selected from optionally substituted C_{1-6} alkyl, optionally substituted carbocycle, and optionally substituted heteroaryl.

[0087] In certain embodiments, for a compound or salt of Formula (IIB), R^{21} is selected from optionally substituted C_{1-3} alkyl, optionally substituted C_{3-6} carbocycle, and optionally substituted 5- or 6-membered heteroaryl; wherein substituents on C_{1-3} alkyl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, and $-CN$, and substituents on C_{3-6} carbocycle and 5- or 6-membered heteroaryl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, and C_{1-6} alkyl optionally substituted with one or more R^{25} .

[0088] In certain embodiments, for a compound or salt of Formula (IIB), R^{21} is selected from optionally substituted C_{1-3} alkyl, optionally substituted C_{3-6} carbocycle and optionally substituted 5- or 6-membered heteroaryl; wherein substituents on C_{1-3} alkyl, C_{3-6} carbocycle and 6-membered heteroaryl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-NO_2$, and $-CN$.

[0089] In certain embodiments, for a compound or salt of Formula (IIB), R^{21} is selected from C_{1-3} alkyl, substituted phenyl, C_5 carbocycle, and optionally substituted pyridyl; wherein substituents on phenyl and pyridyl are selected from halogen, $-OH$, $-NH_2$, $-NO_2$, and $-CN$.

[0090] In certain embodiments, for a compound or salt of Formula (IIB), R^{21} is selected from-



[0091] In certain embodiments, for a compound or salt of Formula (IIB), R^{22} is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, 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^{25} ; and

C₃₋₆ carbocycle optionally substituted with one or more substituents independently selected from: halogen, -OR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -NO₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵.

[0092] In certain embodiments, for a compound or salt of Formula (IIB), R²² is selected from:

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more R²⁵; and

C₃₋₆ carbocycle optionally substituted with one or more substituents independently selected from: halogen, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R²⁵.

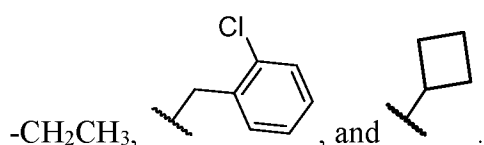
[0093] In certain embodiments, for a compound or salt of Formula (IIB), R²² is selected from:

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more substituents independently selected from halogen; and

C₃₋₆ carbocycle optionally substituted with one or more substituents independently selected from: halogen, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[0094] In certain embodiments, for a compound or salt of Formula (IIB), R²² is selected from C₁₋₃ alkyl and C₃₋₆ carbocycle optionally substituted with one or more halogen.

[0095] In certain embodiments, for a compound or salt of Formula (IIB), R²² is selected from



[0096] In certain embodiments, for a compound or salt of Formula (IIB), R²³ is selected from hydrogen, -OMe, -OH, -NH₂, -COOH, -NO₂, and -CN.

[0097] In certain embodiments, for a compound or salt of Formula (IIB), R²³ is hydrogen.

[0098] In certain embodiments, for a compound or salt of Formula (IIB), R²⁵ is selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), and -CN.

[0099] In certain embodiments, for a compound or salt of Formula (IIB), R²⁵ is selected from

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), and -CN.

[0100] In certain embodiments, for a compound or salt of Formula (IIB), R²⁵ is selected from: halogen, -OR²⁶, -N(R²⁶)₂, =O, -CN, and C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -N(R²⁶)₂, -NO₂, =O, and -CN;

[0101] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is hydrogen.

[0102] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

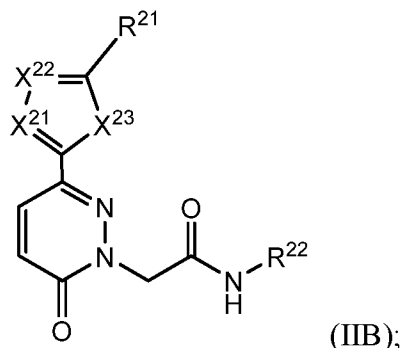
[0103] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[0104] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is selected from C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0105] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is a C₃₋₁₀ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl.

[0106] In certain embodiments, for a compound or salt of Formula (IIB), R²⁶ is a 3- to 10-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl.

[0107] In one aspect, disclosed herein is a compound represented by Formula (IIB):



or a salt thereof, wherein:

X^{21} and X^{22} are independently selected from N and C(R^{23}), wherein at least one of X^{21} and X^{22} is N;

X^{23} is selected from S and O;

R^{21} is selected from optionally substituted C_{1-3} alkyl, optionally substituted phenyl, and optionally substituted 5- or 6-membered heteroaryl; wherein substituents on C_{1-3} alkyl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, and $-CN$, and substituents on phenyl and 5- or 6-membered heteroaryl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, and C_{1-6} alkyl optionally substituted with one or more R^{25} ;

R^{22} is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, 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^{25} ; and

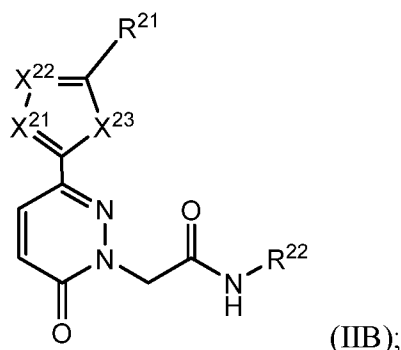
C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from: halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} ;

R^{23} is selected from hydrogen, $-OMe$, $-OH$, $-NH_2$, $-COOH$, $-NO_2$, and $-CN$; and

each R^{25} is independently selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $=O$, $-CN$, and C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-NO_2$, $=O$, and $-CN$;

each R^{26} is independently selected from hydrogen, C_{1-6} alkyl, 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, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$.

[0108] In one aspect, disclosed herein is a compound represented by Formula (IIB):



or a salt thereof, wherein:

X^{21} and X^{22} are independently selected from N and C(R^{23}), wherein at least one of X^{21} and X^{22} is N;

X^{23} is selected from S and O;

R^{21} is selected from C_{1-3} alkyl, substituted phenyl, and optionally substituted 6-membered heteroaryl; wherein substituents on phenyl and 6-membered heteroaryl are selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-NO_2$, and $-CN$;

R^{22} is selected from:

C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more substituents independently selected from halogen; and

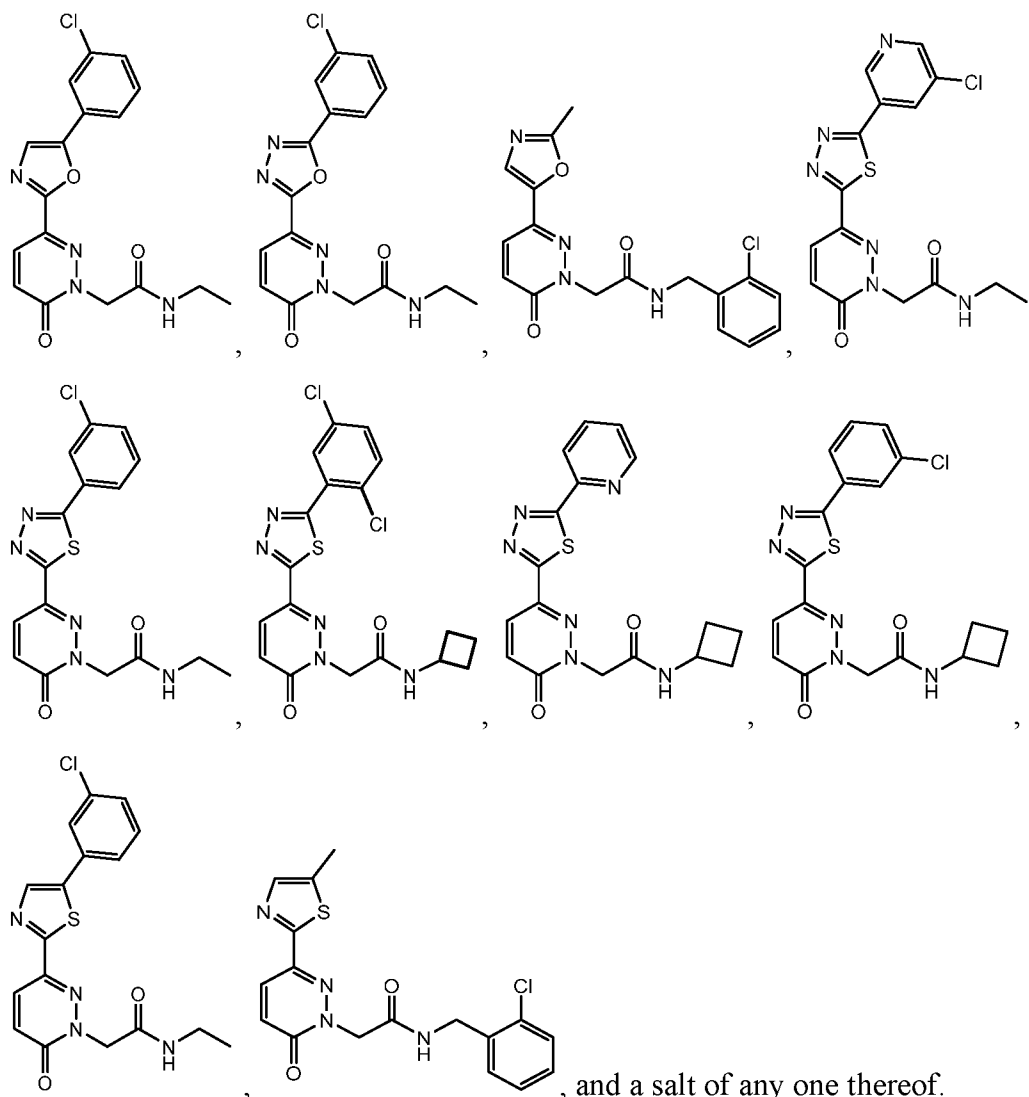
C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from: halogen, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

R^{23} is hydrogen;

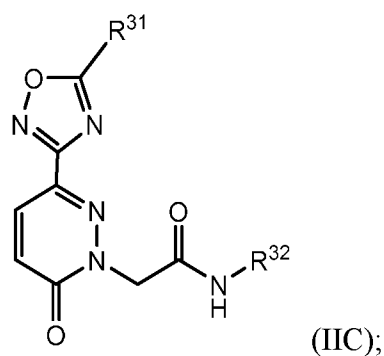
each R^{25} is independently selected from halogen, $-OH$, $-NH_2$, $=O$, $-CN$, and C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OH$, $-NH_2$, $-NO_2$, $=O$, and $-CN$; and

each R^{26} is independently selected from hydrogen, C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$.

[0109] In certain embodiments, the compound or salt of Formula (IIB) is selected from:



[0110] In one aspect, disclosed herein is a compound represented by Formula (IIC):



or a salt thereof, wherein:

R^{31} is selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, -

$N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, 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^{35} ; 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{35} ;

R^{32} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, 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^{35} ; 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{35} ;

each R^{35} is independently selected from:

halogen, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, and $-CN$; and

OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), and -CN;

each R³⁶ is independently selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0111] In certain embodiments, for a compound or salt of Formula (IIC), R³¹ is selected from optionally substituted C₁₋₆ alkyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0112] In certain embodiments, for a compound or salt of Formula (IIC), R³¹ is selected from optionally substituted C₁₋₃ alkyl, optionally substituted phenyl, and optionally substituted 5- or 6-membered heteroaryl; wherein substituents on C₁₋₃ alkyl are selected from halogen, -OR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -NO₂, and -CN, and substituents on phenyl and 5- or 6-membered heteroaryl are selected from halogen, -OR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -NO₂, -CN, and C₁₋₆ alkyl optionally substituted with one or more R³⁵.

[0113] In certain embodiments, for a compound or salt of Formula (IIC), R³¹ is selected from C₁₋₃ alkyl, substituted phenyl, and optionally substituted 6-membered heteroaryl; wherein substituents on phenyl and 6-membered heteroaryl are selected from halogen, -OR³⁶, -N(R³⁶)₂, -NO₂, and -CN.

[0114] In certain embodiments, for a compound or salt of Formula (IIC), R³¹ is selected from C₁₋₃ alkyl, substituted phenyl, and optionally substituted pyridyl; wherein substituents on phenyl and pyridyl are selected from halogen, -OH, -NH₂, -NO₂, and -CN.

[0115] In certain embodiments, for a compound or salt of Formula (IIC), R³² is selected from:

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -NO₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered

heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵; and

C₃₋₆ carbocycle optionally substituted with one or more substituents independently selected from: halogen, -OR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -NO₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵.

[0116] In certain embodiments, for a compound or salt of Formula (IIC), R³² is selected from:

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more R³⁵; and

C₃₋₆ carbocycle optionally substituted with one or more substituents independently selected from: halogen, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R³⁵.

[0117] In certain embodiments, for a compound or salt of Formula (IIC), R³² is C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more substituents independently selected from halogen

[0118] In certain embodiments, for a compound or salt of Formula (IIC), R³² is selected from C₁₋₃ alkyl.

[0119] In certain embodiments, for a compound or salt of Formula (IIC), R³² is selected from -CH₂CH₃.

[0120] In certain embodiments, for a compound or salt of Formula (IIC), R³⁵ is selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), and -CN.

[0121] In certain embodiments, for a compound or salt of Formula (IIC), R³⁵ is selected from C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -SR³⁶, -N(R³⁶)₂, -C(O)R³⁶, -C(O)N(R³⁶)₂, -N(R³⁶)C(O)R³⁶, -N(R³⁶)C(O)N(R³⁶)₂, -OC(O)N(R³⁶)₂, -N(R³⁶)C(O)OR³⁶, -C(O)OR³⁶, -OC(O)R³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -NO₂, =O, =S, =N(R³⁶), and -CN.

[0122] In certain embodiments, for a compound or salt of Formula (IIC), R³⁵ is selected from: halogen, -OR³⁶, -N(R³⁶)₂, =O, -CN, and C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR³⁶, -N(R³⁶)₂, -NO₂, =O, and -CN;

[0123] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is hydrogen.

[0124] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =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.

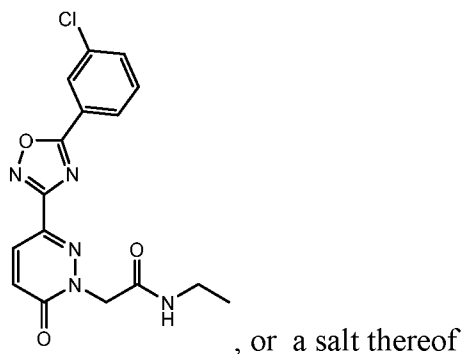
[0125] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O- C_{1-6} alkyl, -S- C_{1-6} alkyl, -N(C_{1-6} alkyl)₂, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[0126] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is selected from 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, -NO₂, -NH₂, =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.

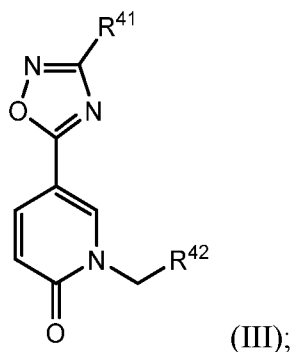
[0127] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is a C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O- C_{1-6} alkyl, -S- C_{1-6} alkyl, -N(C_{1-6} alkyl)₂, -NH(C_{1-6} alkyl), C_{1-6} alkyl, and haloalkyl.

[0128] In certain embodiments, for a compound or salt of Formula (IIC), R^{36} is a 3- to 10-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =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, and haloalkyl.

[0129] In certain embodiments, the compound or salt of Formula (IIC) is selected from:



[0130] In some embodiments, disclosed herein is a compound represented by Formula (III):

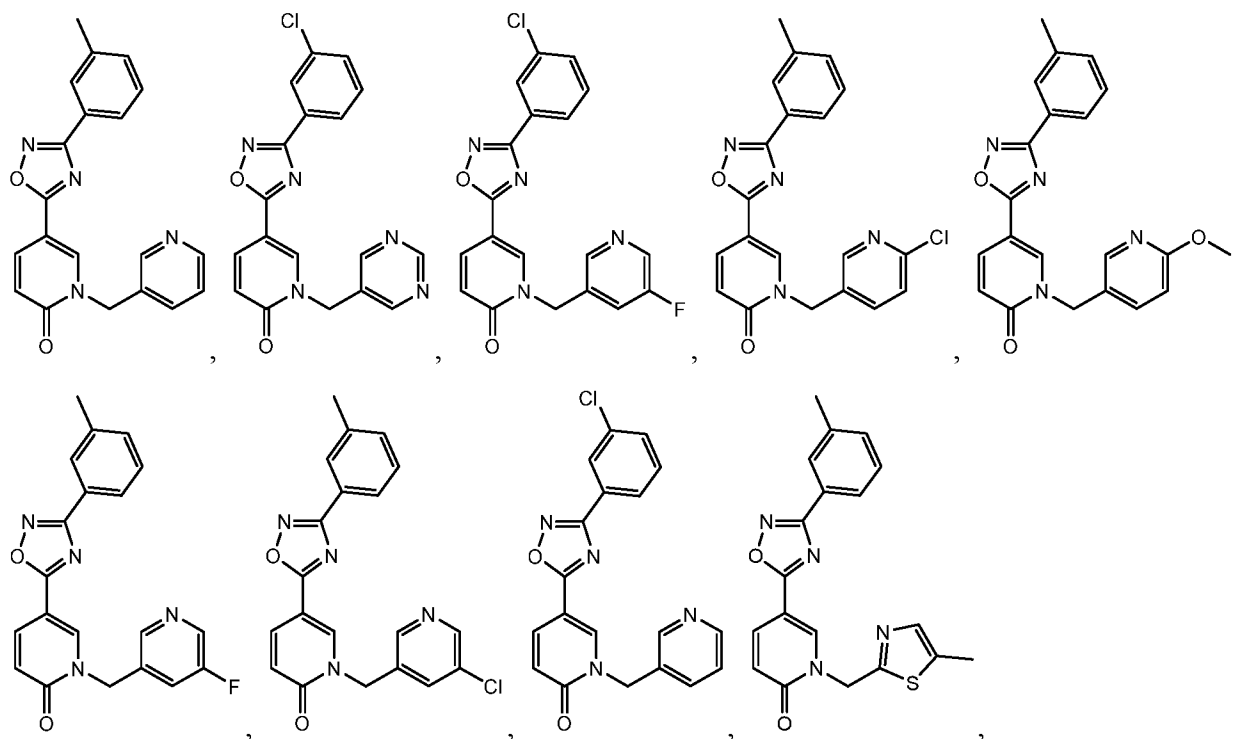


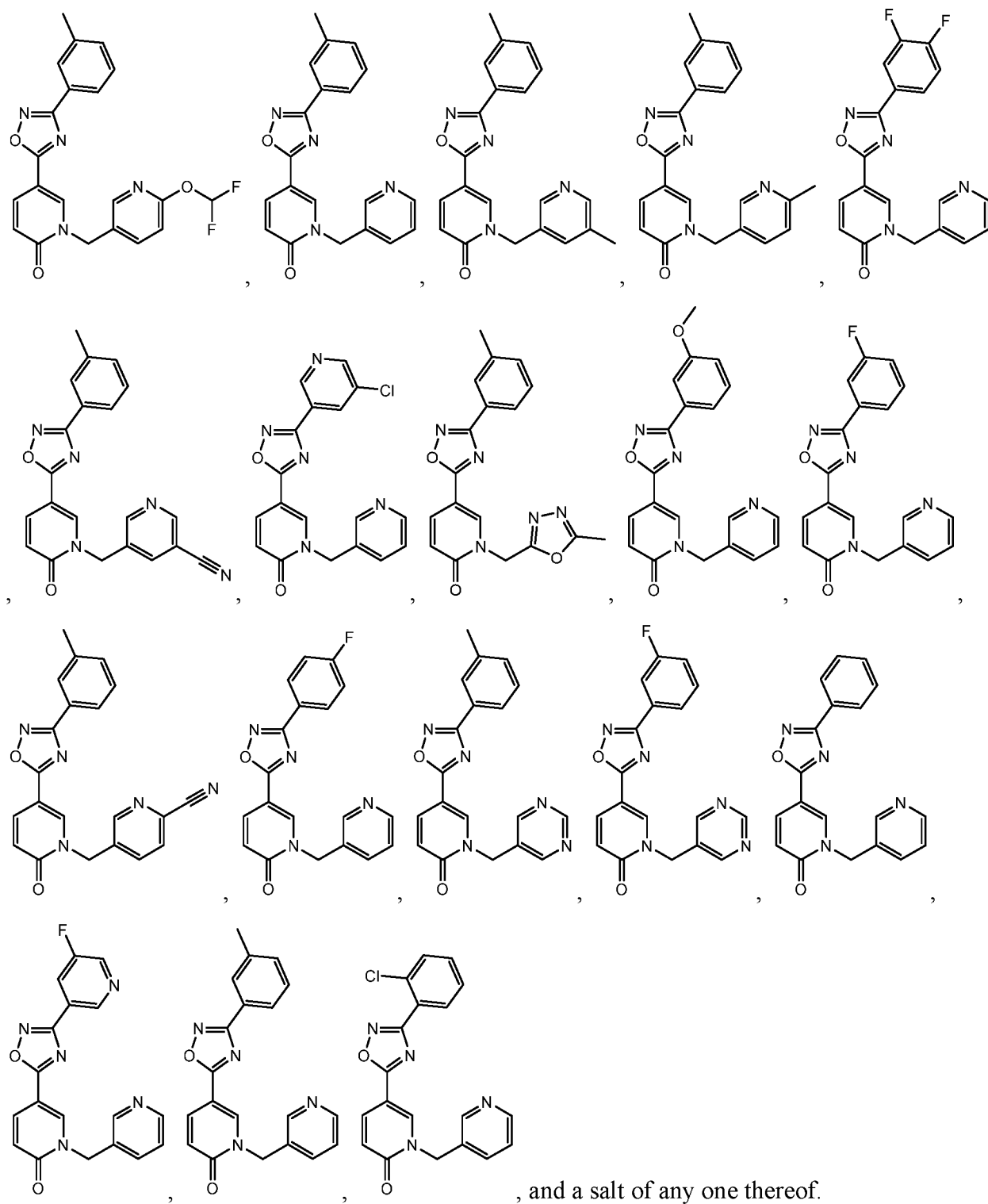
or a salt thereof, wherein:

R⁴¹ is selected from phenyl and pyridyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH₂, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxide, and C₁₋₆ haloalkoxide;

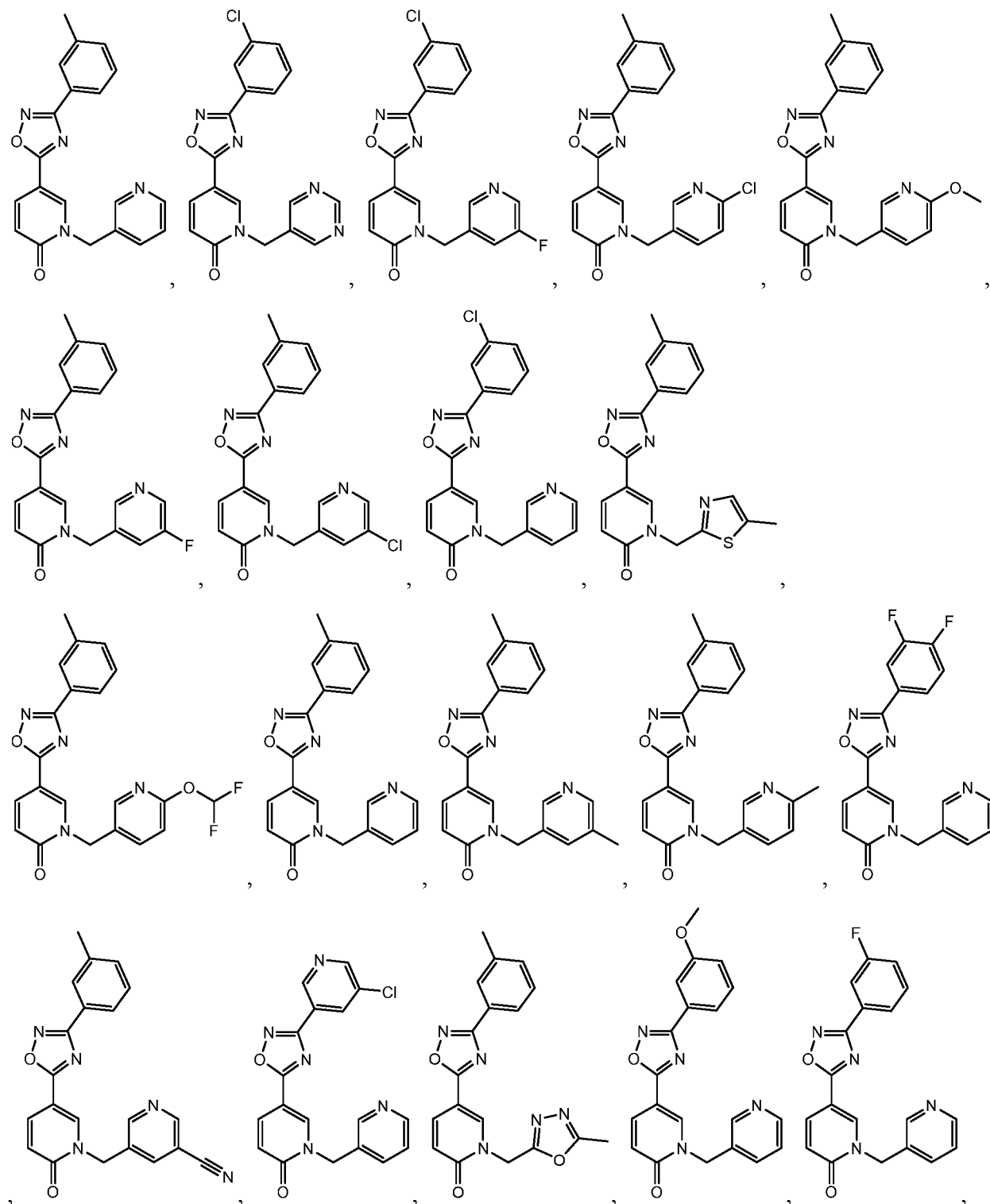
R⁴² is a 5- to 6- membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH₂, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxide, and C₁₋₆ haloalkoxide.

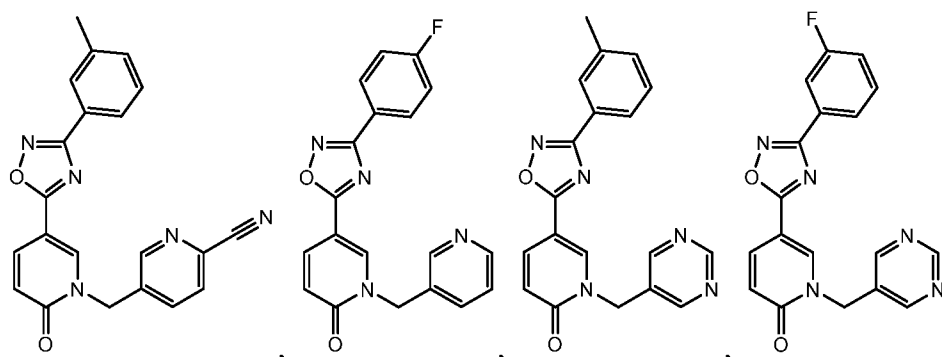
[0131] In certain embodiments, for a compound or salt of Formula (III) is selected from





[0132] In certain embodiments, for a compound or salt of Formula (III) is selected from



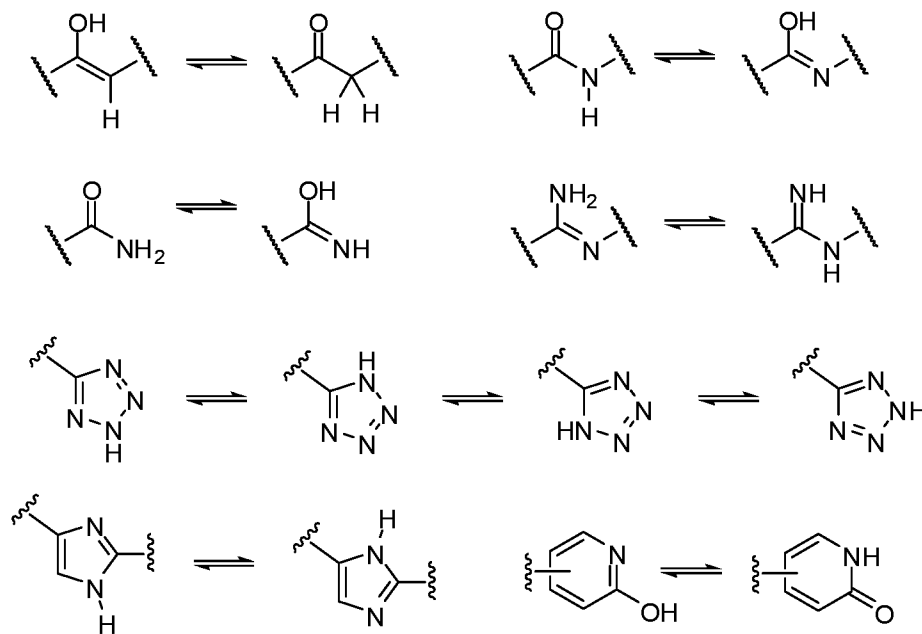


, and a salt of any one

thereof.

[0133] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, compounds described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[0134] A “tautomer” refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0135] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^2H , ^3H , ^{11}C , ^{13}C and/or ^{14}C . In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in

U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[0136] Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of the present disclosure.

[0137] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^2H , ^{11}C , ^{13}C , ^{14}C , ^{15}C , ^{12}N , ^{13}N , ^{15}N , ^{16}N , ^{16}O , ^{17}O , ^{14}F , ^{15}F , ^{16}F , ^{17}F , ^{18}F , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , and ^{125}I are all contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0138] In certain embodiments, the compounds disclosed herein have some or all of the ^1H atoms replaced with ^2H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[0139] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[0140] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[0141] Compounds of the present invention also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0142] Included in the present disclosure are salts, particularly pharmaceutically acceptable salts, of the compounds described herein. The compounds of the present disclosure that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as bromide, chloride, or fluoride, particularly bromide.

[0143] The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, “Enantiomers, Racemates and Resolutions”, John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

[0144] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, in some embodiments, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[0145] In certain embodiments, compounds or salts of the compounds may be prodrugs, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or carboxylic acid present in the parent compound is presented as an ester. The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into pharmaceutical agents of the present disclosure. One method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal such as specific target cells in the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids and esters of phosphonic acids) are preferred prodrugs of the present disclosure.

[0146] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound as set forth herein are included within the scope of the claims. In

some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[0147] Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. Prodrugs may help enhance the cell permeability of a compound relative to the parent drug. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues or to increase drug residence inside of a cell.

[0148] In some embodiments, the design of a prodrug increases the lipophilicity of the pharmaceutical agent. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak *et al.*, *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al.*, *Gastroenterol.*, 106:405-413 (1994); Hochhaus *et al.*, *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen *et al.*, *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula *et al.*, *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein for such disclosure). According to another embodiment, the present disclosure provides methods of producing the above-defined compounds. The compounds may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

[0149] Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations* (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed. (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis* (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis* (1995).

Therapeutic Applications

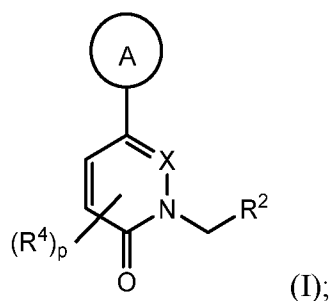
[0150] Methods of administration of a compound or salt of Formula (I), (IIA), (IIB), (IIC), or (III) discussed herein may be used for inhibiting muscle myosin II. In some embodiments, the compounds and salts thereof may be used to treat activity-induced muscle damage. In some

embodiments, the compounds may be used to treat neuromuscular conditions and movement disorders (such as spasticity).

[0151] Methods of administration of a compound or salt of Formula (I), (IIA), (IIB), (IIC), or (III) discussed herein may be used for the treatment of neuromuscular conditions and movement disorders. Examples of neuromuscular conditions include but are not limited to Duchenne Muscular Dystrophy, Becker muscular dystrophy, myotonic dystrophy 1, myotonic dystrophy 2, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, limb girdle muscular dystrophies, tendinitis and carpal tunnel syndrome. Examples of movement disorders include but are not limited to muscle spasticity disorders, spasticity associated with multiple sclerosis, Parkinson's disease, Alzheimer's disease, or cerebral palsy, or injury or a traumatic event such as stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, or amyotrophic lateral sclerosis. Also included are other conditions that may respond to the inhibition of skeletal myosin II, skeletal troponin C, skeletal troponin I, skeletal tropomyosin, skeletal troponin T, skeletal regulatory light chains, skeletal myosin binding protein C or skeletal actin. In some embodiments, neuromuscular conditions and movement disorders are selected from muscular dystrophies and myopathies. In some embodiments, muscular dystrophies are diseases that cause progressive weakness and loss of muscle mass where abnormal genes (mutations) interfere with the production of proteins needed to form healthy muscle. In some embodiments, muscular dystrophies are selected from Becker muscular dystrophy (BMD), Congenital muscular dystrophies (CMD), Duchenne muscular dystrophy (DMD), Emery-Dreifuss muscular dystrophy (EDMD), Facioscapulohumeral muscular dystrophy (FSHD), Limb-girdle muscular dystrophies (LGMD), Myotonic dystrophy (DM), and Oculopharyngeal muscular dystrophy (OPMD). In some embodiments, Congenital muscular dystrophies (CMD) is selected from Bethlem CMD, Fukuyama CMD, Muscle-eye-brain diseases (MEBs), Rigid spine syndromes, Ullrich CMD, and Walker-Warburg syndromes (WWS). In some embodiments, myopathies are diseases of muscle that are not caused by nerve disorders. Myopathies cause the muscles to become weak or shrunken (atrophied). In some embodiments, myopathies are selected from congenital myopathies, distal myopathies, endocrine myopathies, inflammatory myopathies, metabolic myopathies, myofibrillar myopathies (MFM), scapuloperoneal myopathy, and cardiomyopathies. In some embodiments, congenital myopathies are selected from cap myopathies, centronuclear myopathies, congenital myopathies with fiber type disproportion, core myopathies, central core disease, multiminicore myopathies, myosin storage myopathies, myotubular myopathy, and nemaline myopathies. In some embodiments, distal myopathies are selected from, gne myopathy/Nonaka myopathy/hereditary inclusion-body

myopathy (HIBM), laing distal myopathy, Markesbery-Griggs late-onset distal myopathy, Miyoshi myopathy, Udd myopathy/tibial muscular dystrophy, VCP myopathy / IBMPFD, vocal cord and pharyngeal distal myopathy, and welander distal myopathy. In some embodiments, endocrine myopathies are selected from, hyperthyroid myopathy, and hypothyroid myopathy. In some embodiments, inflammatory myopathies are selected from, dermatomyositis, inclusion-body myositis, and polymyositis. In some embodiments, metabolic myopathies are selected from, von Gierke's disease, Anderson disease, Fanconi-Bickel syndrome, aldolase A deficiency, acid maltase deficiency (Pompe disease), carnitine deficiency, carnitine palmitoyltransferase deficiency, debrancher enzyme deficiency (Cori disease, Forbes disease), lactate dehydrogenase deficiency, myoadenylate deaminase deficiency, phosphofructokinase deficiency (Tarui disease), phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency (Her's disease), and phosphorylase deficiency (McArdle disease). In some embodiments, cardiomyopathies are selected from intrinsic cardiomyopathies and extrinsic cardiomyopathies. In some embodiments, intrinsic cardiomyopathies are selected from genetic myopathies and acquired myopathies. In some embodiments, genetic myopathies are selected from Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), LV non-compaction, ion channelopathies, dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM). In some embodiments, acquired myopathies are selected from stress cardiomyopathy, myocarditis, eosinophilic myocarditis, and ischemic cardiomyopathy. In some embodiments, extrinsic cardiomyopathies are selected from metabolic cardiomyopathies, endomyocardial cardiomyopathies, endocrine cardiomyopathies, and cardiofacial cardiomyopathies. In some embodiments, metabolic cardiomyopathies are selected from Fabry's disease and hemochromatosis. In some embodiments, endomyocardial cardiomyopathies are selected from endomyocardial fibrosis and Hypereosinophilic syndrome. In some embodiments, endocrine cardiomyopathies are selected from diabetes mellitus, hyperthyroidism, and acromegaly. In some embodiments, the Cardiofacial cardiomyopathy is Noonan syndrome.

[0152] In some embodiments, disclosed herein are methods to treat neuromuscular and movement disorders by the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC). In some embodiments, disclosed herein are methods to treat neuromuscular and movement disorders by the administration of a compound or salt of Formula (I);



or a salt thereof, wherein:

the A ring is selected from a 5-membered heteroaromatic ring optionally substituted by one or more substituents independently selected from R^1 ;

X is N or CH;

each R^1 is independently selected from:

halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, and $-CN$;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, 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^5 ; 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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ;

R^2 is selected from:

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

=N(R⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and -C(O)NR⁷R⁸;

each R⁴ is independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, -CN, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, and -CN;

each R⁵ is independently selected from:

halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN;

each R⁶ is independently selected from:

hydrogen; and

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

R^7 is selected from hydrogen and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-NO_2$, and $-CN$;

R^8 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, 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^5 ;

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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ; and

p is 0, 1, or 2.

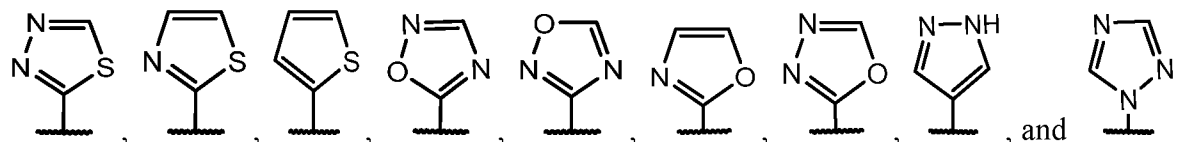
[0153] In certain embodiments, for a compound or salt of Formula (I), A ring is an unsubstituted 5-membered heteroaromatic ring.

[0154] In certain embodiments, for a compound or salt of Formula (I), A ring is a 5-membered heteroaromatic ring substituted by one or more substituents independently selected from R^1 . In certain embodiments, A ring has two or more heteroatoms. In certain embodiments, A ring has three heteroatoms.

[0155] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from thiophene, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, tetrazole, and furan, each of which is optionally substituted with one or more substituents independently selected from R^1 .

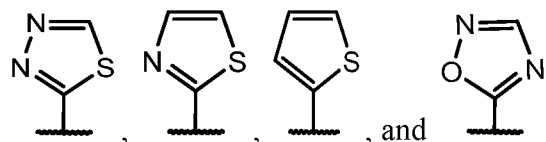
[0156] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from thiophene, oxadiazole, oxazole, thiadiazole, triazole, pyrazole, and thiazole, each of which is optionally substituted with one or more substituents independently selected from R^1 .

[0157] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from



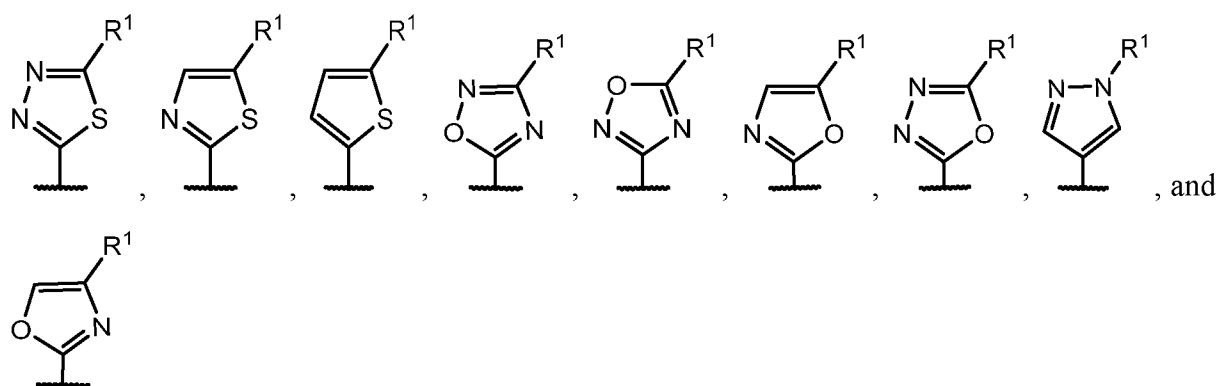
each of which is optionally substituted with one or more substituents independently selected from R^1 .

[0158] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from

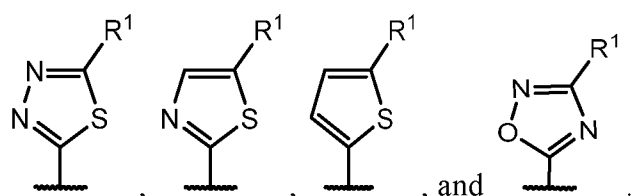


each of which is optionally substituted with one or more substituents independently selected from R^1 .

[0159] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from



[0160] In certain embodiments, for a compound or salt of Formula (I), A ring is selected from



[0161] In certain embodiments, for a compound or salt of Formula (I), X is N. In certain embodiments, for a compound or salt of Formula (I), X is CH.

[0162] In certain embodiments, for a compound or salt of Formula (I), R^1 is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-CN$, 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^5 ; 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, $-OR^6$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle;

wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

[0163] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from:

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, and -CN; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, - and C₁₋₆ alkyl, optionally substituted with one or more R⁵.

[0164] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from:

C₁₋₆ alkyl; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, - and C₁₋₆ alkyl optionally substituted with one or more R⁵.

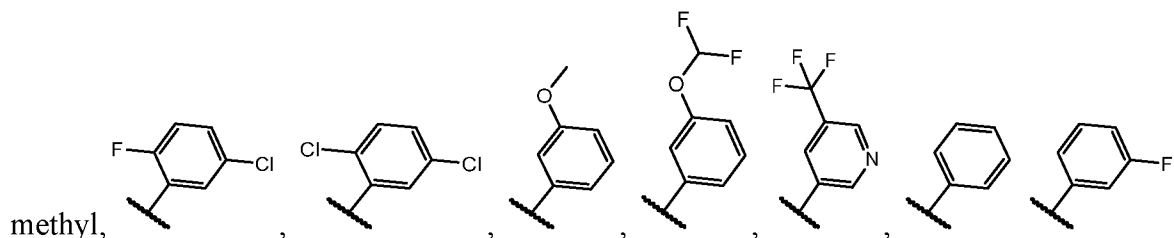
[0165] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from C₁₋₆ alkyl optionally substituted with halogen or -OR⁶; and C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, - and C₁₋₆ alkyl optionally substituted with one or more R⁵.

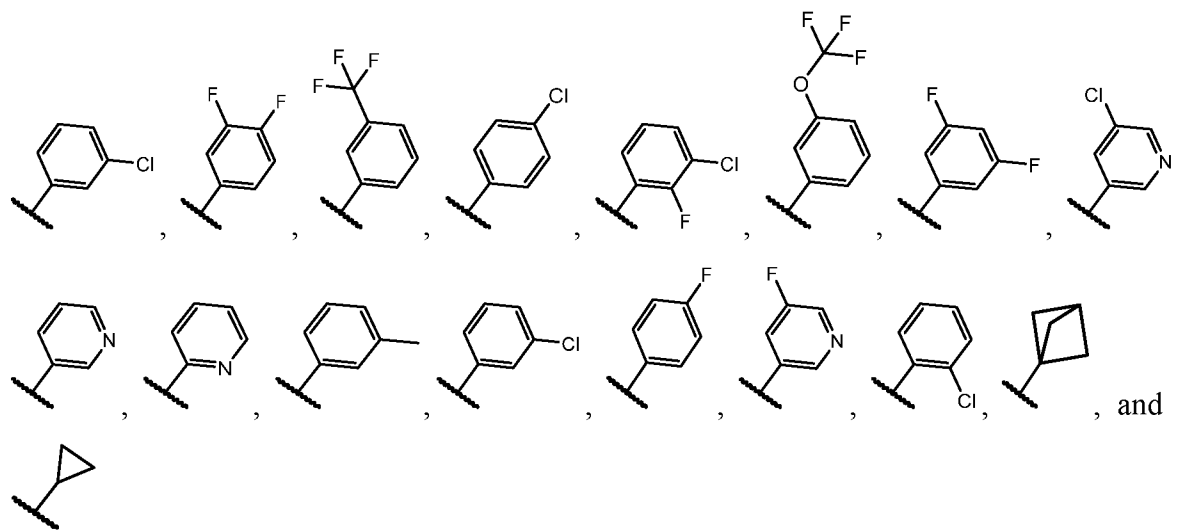
[0166] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen and -OR⁶.

[0167] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from methyl optionally substituted with one or more substituents independently selected from halogen, -OH, -OC₆H₅, and -OCH₃.

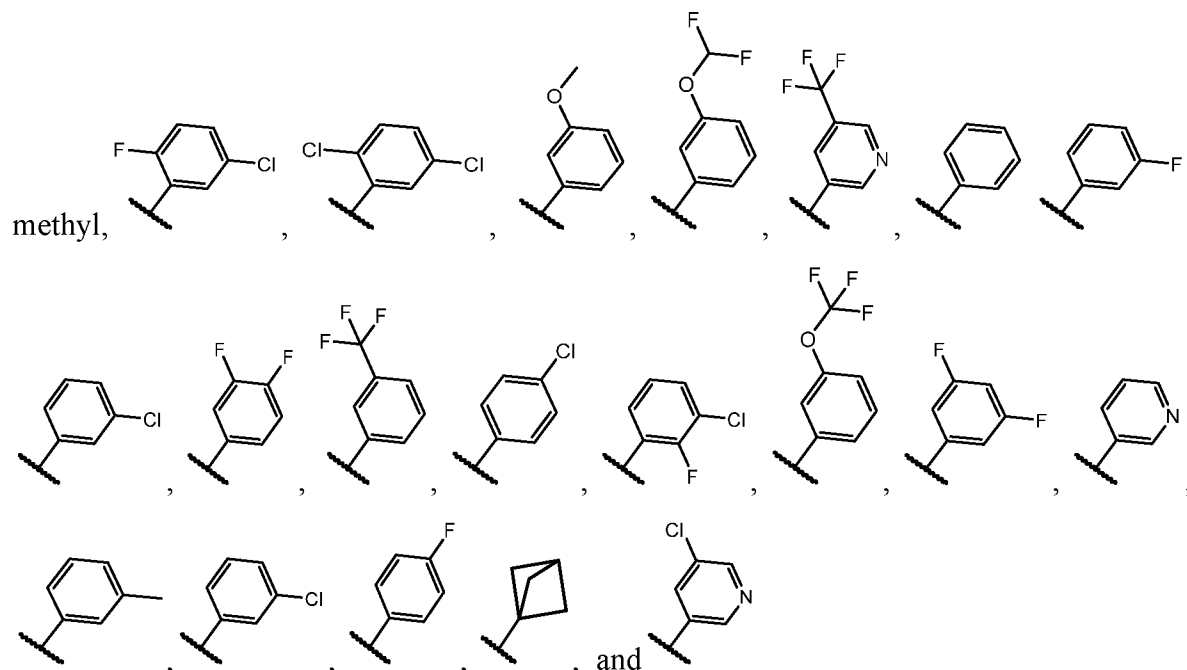
[0168] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from pyridine, C₃₋₅ cycloalkyl, and phenyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CH₃, -CN, -OH, -OCH₃, -OCF₃, -CF₃, -CHF₂, -OCHF₂, and cyclopropyl.

[0169] In certain embodiments, for a compound or salt of Formula (I), R¹ is selected from





[0170] In certain embodiments, for a compound or salt of Formula (I), R^1 is selected from



[0171] In certain embodiments, for a compound or salt of Formula (I), R^2 is selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-CN$, 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^5 .

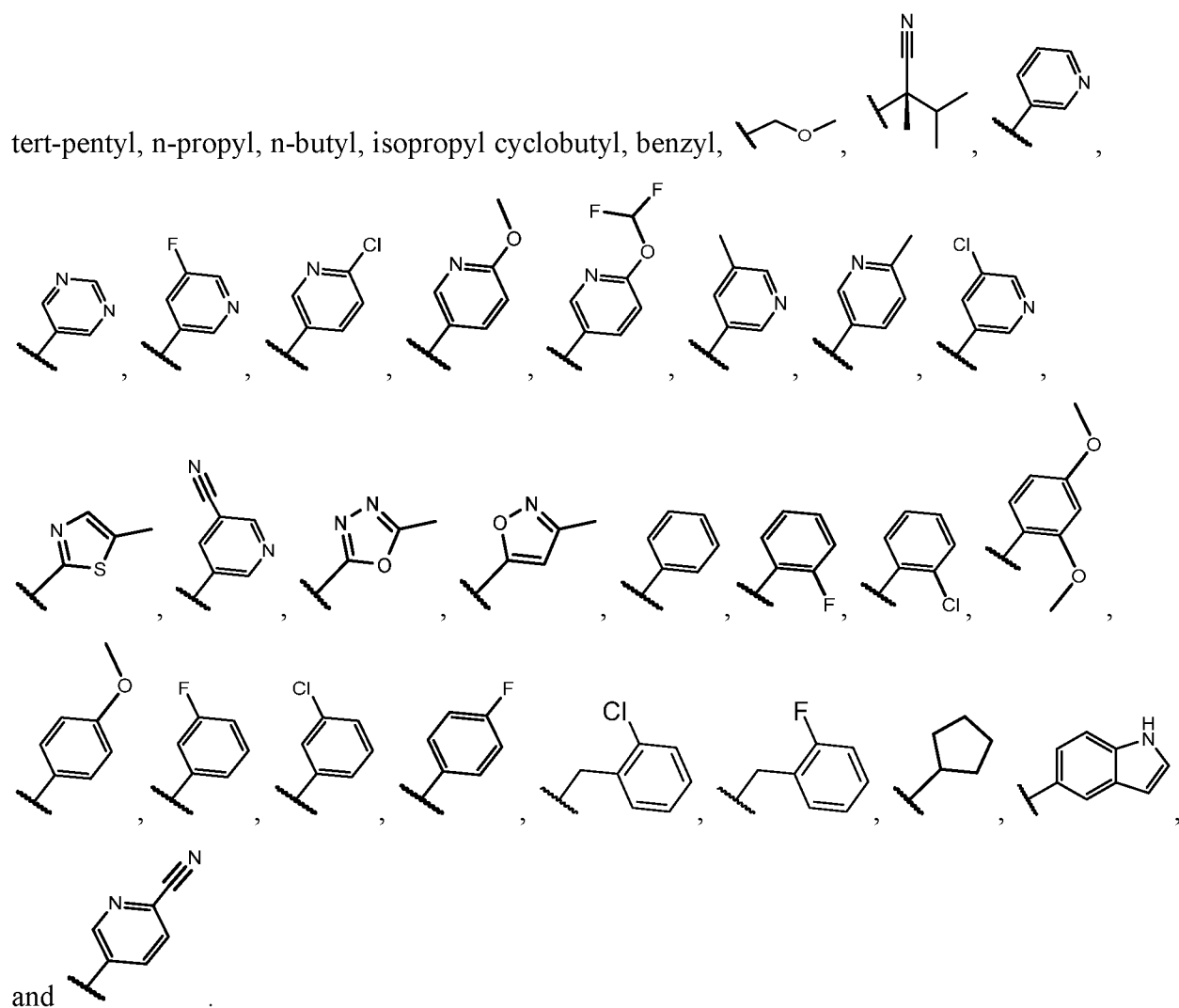
[0172] In certain embodiments, for a compound or salt of Formula (I), R^2 is selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, and $-CN$.

[0173] In certain embodiments, for a compound or salt of Formula (I), R^2 is selected from 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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, CN , C_{1-6} alkyl,

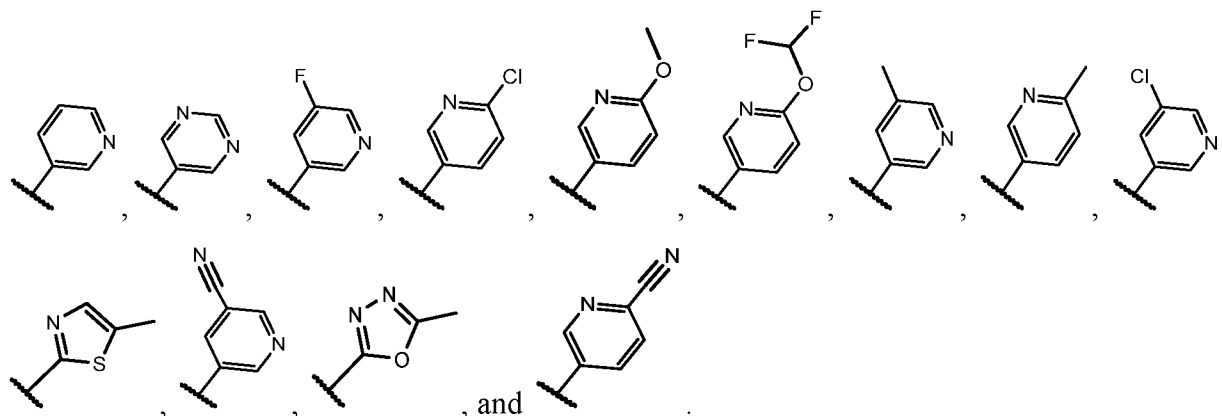
C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

[0174] In certain embodiments, for a compound or salt of Formula (I), R² is selected from phenyl, pyridyl, pyrimidyl, thiazole, oxadiazole, and oxazole, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, CN, and C₁₋₆ alkyl.

[0175] In certain embodiments, for a compound or salt of Formula (I), R² is selected from ethyl,



[0176] In certain embodiments, for a compound or salt of Formula (I), R^2 is selected from



[0177] In certain embodiments, for a compound or salt of Formula (I), R^2 is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -OMe, -NH₂, and CN;

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, -OH, -SH, -NH₂, -CN, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and -C(O)NR⁷R⁸.

[0178] In certain embodiments, for a compound or salt of Formula (I), R^2 is -C(O)NR⁷R⁸.

[0179] In certain embodiments, for a compound or salt of Formula (I), R^4 is selected from halogen, -OH, -OMe, -SH, -N(H)₂, -NO₂, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -OMe, -SH, -N(H)₂, -NO₂, and -CN.

[0180] In certain embodiments, for a compound or salt of Formula (I), R^4 is selected from halogen, -OH, -OMe, -SH, -N(H)₂, -NO₂, and -CN.

[0181] In certain embodiments, for a compound or salt of Formula (I), R^5 is selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN.

[0182] In certain embodiments, for a compound or salt of Formula (I), R^5 is selected from 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, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN.

[0183] In certain embodiments, for a compound or salt of Formula (I), R^5 is selected from halogen, $-OR^6$, $-N(R^6)_2$, $=O$, $-CN$, and C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-N(R^6)_2$, $-NO_2$, $=O$, and $-CN$;

[0184] In certain embodiments, for a compound or salt of Formula (I), R^6 is hydrogen.

[0185] In certain embodiments, for a compound or salt of Formula (I), R^6 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[0186] In certain embodiments, for a compound or salt of Formula (I), R^6 is selected from C_{1-6} alkyl 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[0187] In certain embodiments, for a compound or salt of Formula (I), R^6 is selected from 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

[0188] In certain embodiments, for a compound or salt of Formula (I), R^6 is a C_{3-10} carbocycle 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{1-6} alkyl, and haloalkyl.

[0189] In certain embodiments, for a compound or salt of Formula (I), R^6 is a phenyl 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{1-6} alkyl, and haloalkyl.

[0190] In certain embodiments, for a compound or salt of Formula (I), R^6 is a phenyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$.

[0191] In certain embodiments, for a compound or salt of Formula (I), R^6 is a 3- to 10-membered heterocycle 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, $-N(C_{1-6} \text{ alkyl})_2$, $-NH(C_{1-6} \text{ alkyl})$, C_{1-6} alkyl, and haloalkyl.

[0192] In certain embodiments, for a compound or salt of Formula (I), R^6 is a 5- to 6-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl

[0193] In certain embodiments, for a compound or salt of Formula (I), R^6 is a 5 membered heterocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl

[0194] In certain embodiments, for a compound or salt of Formula (I), R^7 is selected from hydrogen and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH₂, -NO₂, and -CN.

[0195] In certain embodiments, for a compound or salt of Formula (I), R^7 is selected from R^7 is selected from hydrogen and C₁₋₃ alkyl.

[0196] In certain embodiments, for a compound or salt of Formula (I), R^7 is hydrogen.

[0197] In certain embodiments, for a compound or salt of Formula (I), R^8 is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

[0198] In certain embodiments, for a compound or salt of Formula (I), R^8 is selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

[0199] In certain embodiments, for a compound or salt of Formula (I), R^8 is selected from methyl, ethyl, propyl, and butyl, each of which is optionally substituted with one or more halogen, -OH, -CN, -OCH₃, -CF₃, -CHF₂, -CH₂F, phenyl, or pyridyl, wherein the phenyl or pyridyl is optionally substituted with halogen, -CH₃, -OH, -OCH₃, -CF₃, -CHF₂, or -CH₂F.

[0200] In certain embodiments, for a compound or salt of Formula (I), R^8 is selected from

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

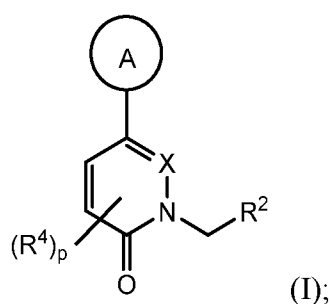
[0201] In certain embodiments, for a compound or salt of Formula (I), R⁸ is selected from C₃₋₆ carbocycle and 5- to 9-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

[0202] In certain embodiments, for a compound or salt of Formula (I), R⁸ is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, and furan, each of which is optionally substituted with one or more R⁵.

[0203] In certain embodiments, for a compound or salt of Formula (I), R⁸ is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, and each of which is optionally substituted with one or more R⁵.

[0204] In certain embodiments, for a compound or salt of Formula (I), R⁸ is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, and each of which is optionally substituted with one or more halogen, -CN, -OH, -OCH₃, -CF₃, -CHF₂, or -CH₂F.

[0205] In some embodiments, disclosed herein are methods to treat neuromuscular and movement disorders by the administration of a compound or salt of Formula (I);



or a salt thereof, wherein:

A ring is selected from thiophene, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, tetrazole, and furan, each of which is optionally substituted with one or more substituents independently selected from R¹;

X is N or CH;

each R¹ is independently selected from:

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

R² is selected from

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

-C(O)NR⁷R⁸;

each R⁴ is independently selected from halogen, -OH, -OMe, -SH, -NH₂, -NO₂, -CN, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -OMe, -SH, -N(H)₂, -NO₂, and -CN

each R⁵ is independently selected from:

halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, =O, =S, and -CN; and

C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, =O, =S, and -CN;

each R⁶ is independently selected from:

hydrogen;

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

R⁷ is selected from hydrogen and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH₂, -NO₂, and -CN.

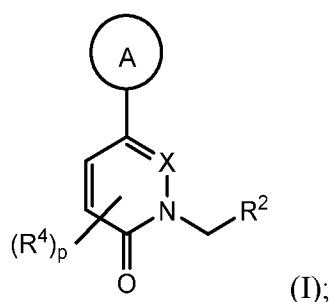
R⁸ is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

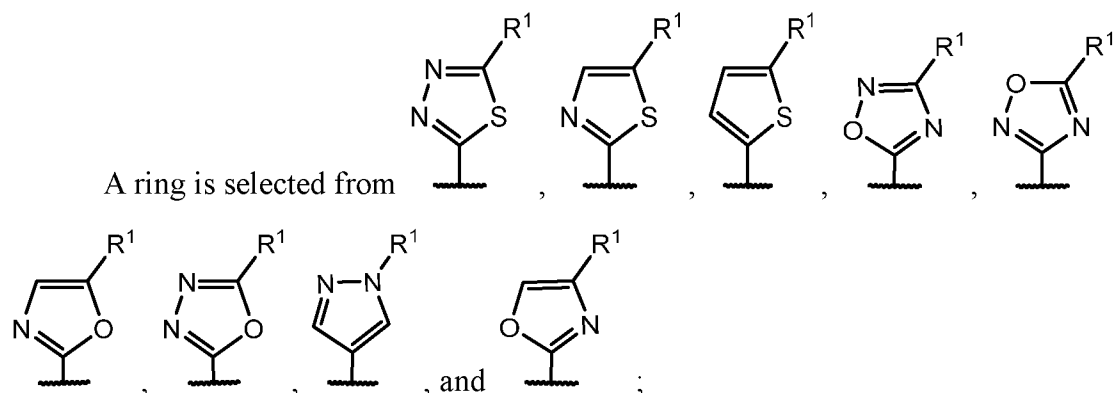
C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

p is 0.

[0206] In some embodiments, disclosed herein are methods to treat neuromuscular and movement disorders by the administration of a compound or salt of Formula (I);



or a salt thereof, wherein:



X is N or CH;

each R^1 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, and $-CN$; 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, $-OR^6$, - and C_{1-6} alkyl, optionally substituted with one or more R^5 ;

R^2 is selected from

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OH$, $-OMe$, $-NH_2$, and CN ;

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, $-OH$, $-SH$, $-NH_2$, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxide, C_{1-6} haloalkoxide, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and $-C(O)NR^7R^8$;

each R^4 is independently selected from halogen, $-OH$, $-OMe$, $-SH$, $-NH_2$, $-NO_2$, and $-CN$;

each R^5 is independently selected from halogen, $-OH$, $-OMe$, $-NH_2$, $=O$, $-CN$, and C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OH$, $-OMe$, $-NH_2$, $-NO_2$, $=O$, and $-CN$;

each R^6 is independently selected from:

hydrogen;

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

C₃₋₁₀ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, and haloalkyl

R⁷ is selected from hydrogen and C₁₋₃ alkyl optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH₂, -NO₂, and -CN.

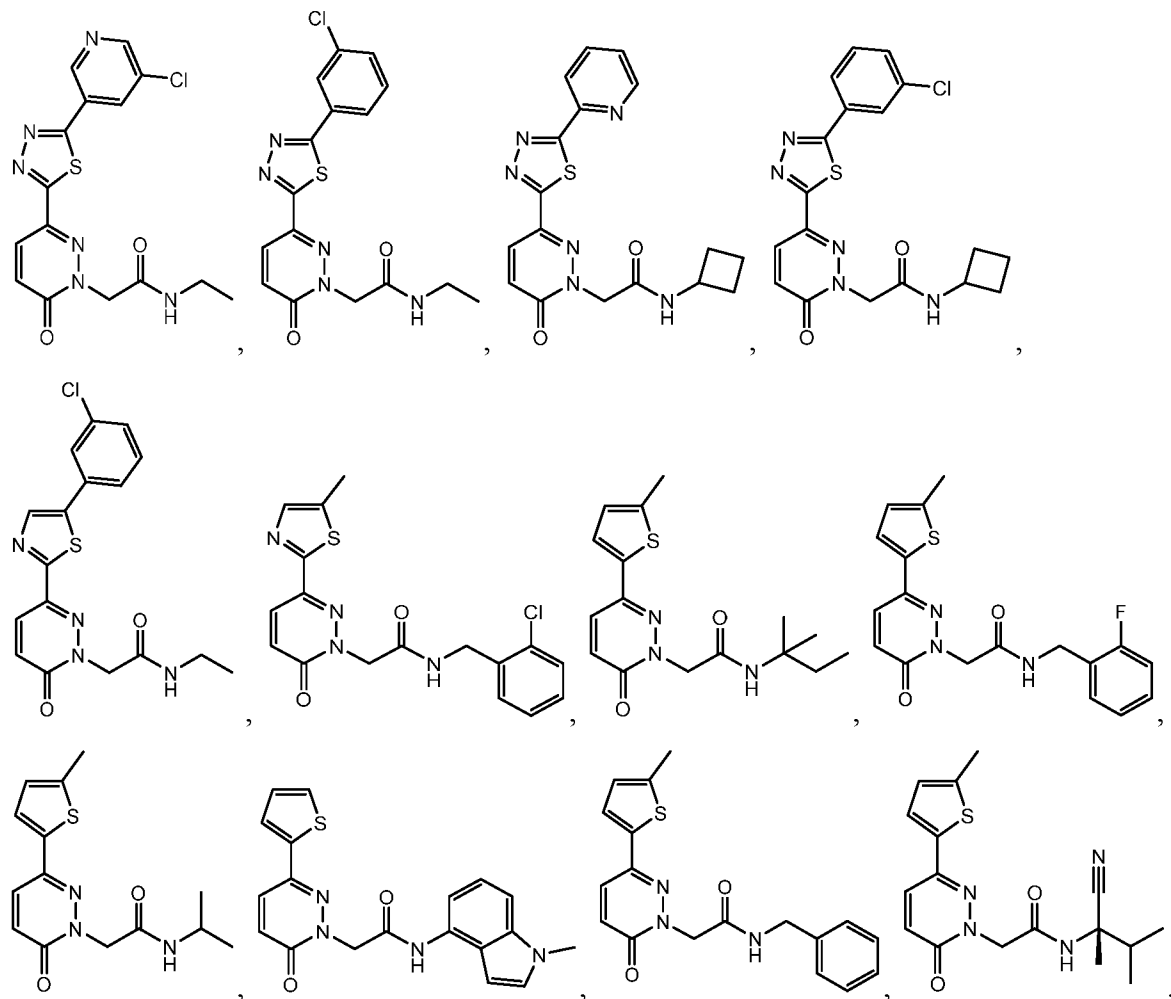
R⁸ is selected from:

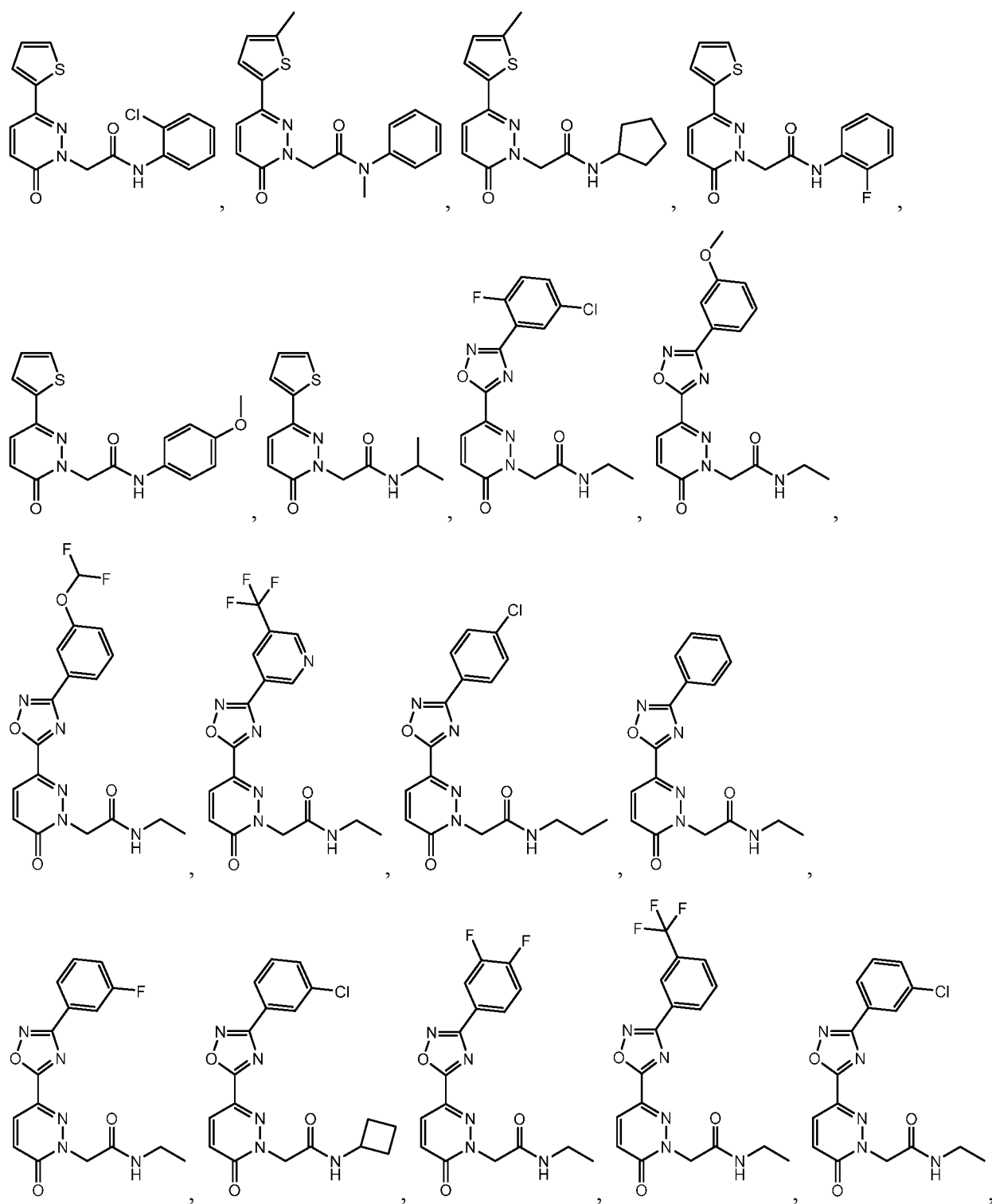
methyl, ethyl, propyl, and butyl, each of which is optionally substituted with one or more halogen, -OH, -CN, -OCH₃, -CF₃, -CHF₂, -CH₂F, phenyl, or pyridyl, wherein the phenyl or pyridyl is optionally substituted with halogen, -CH₃, -OH, -OCH₃, -CF₃, -CHF₂, or -CH₂F; and

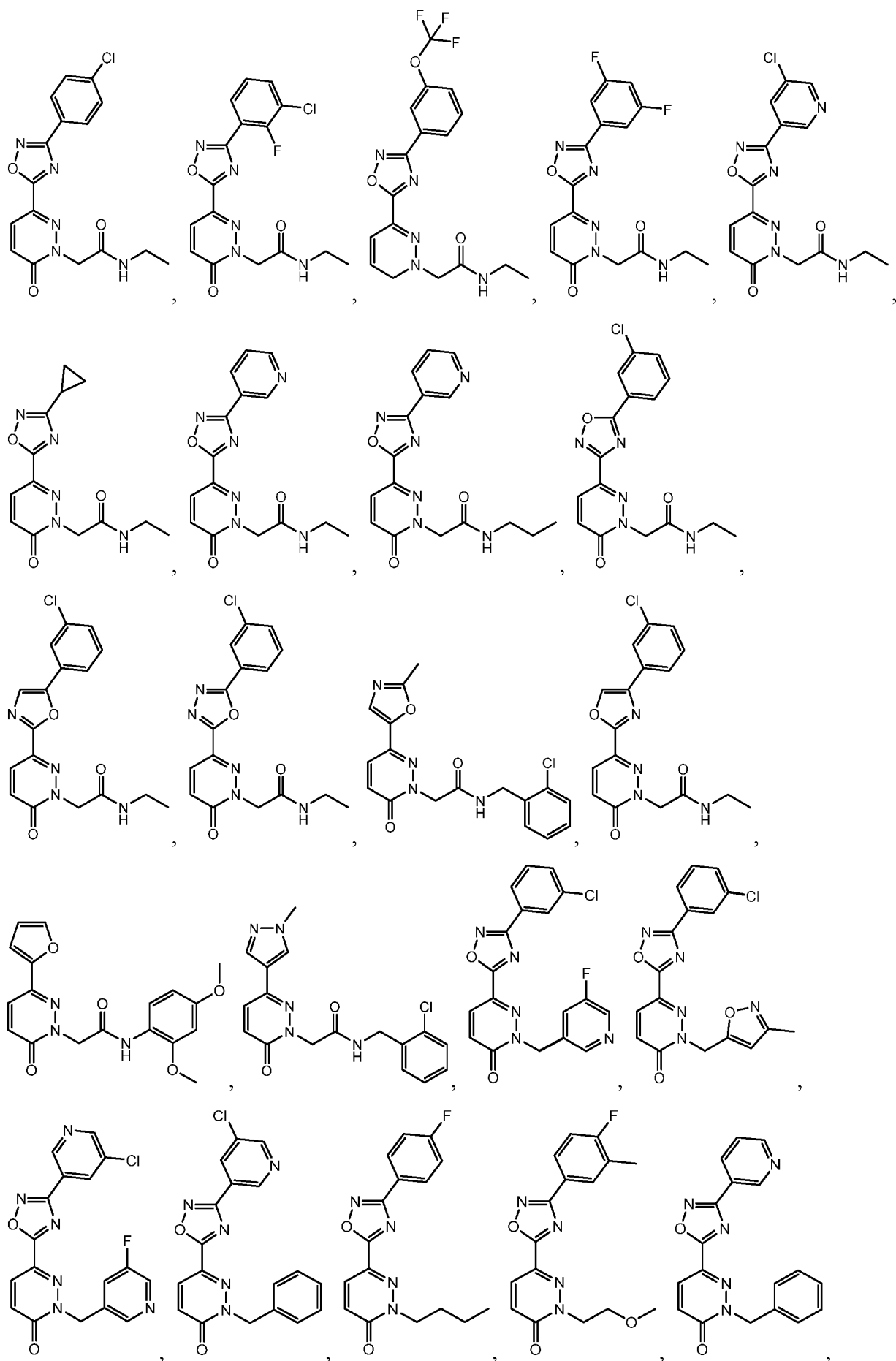
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, and furan, each of which is optionally substituted with one or more halogen, -CN, -OH, -OCH₃, -CF₃, -CHF₂, or -CH₂F; and

p is 0.

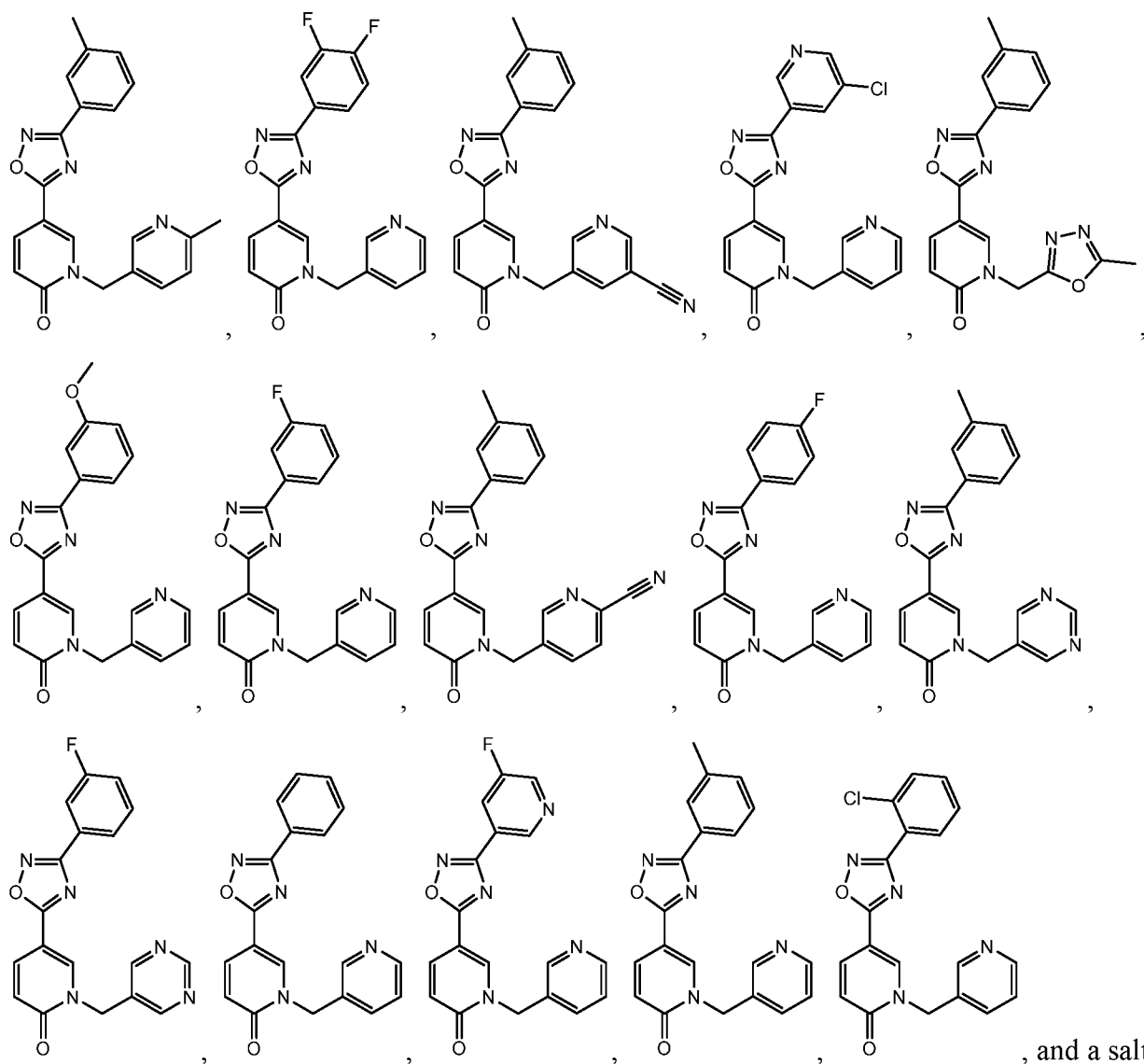
[0207] In certain embodiments, for a compound or salt of Formula (I) is selected from





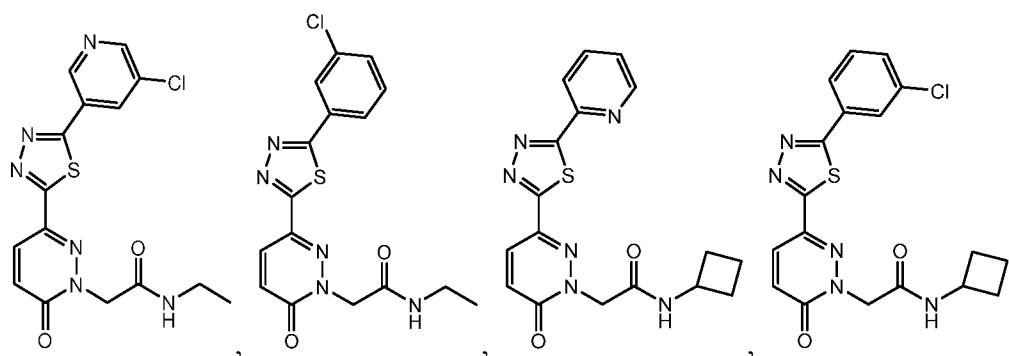


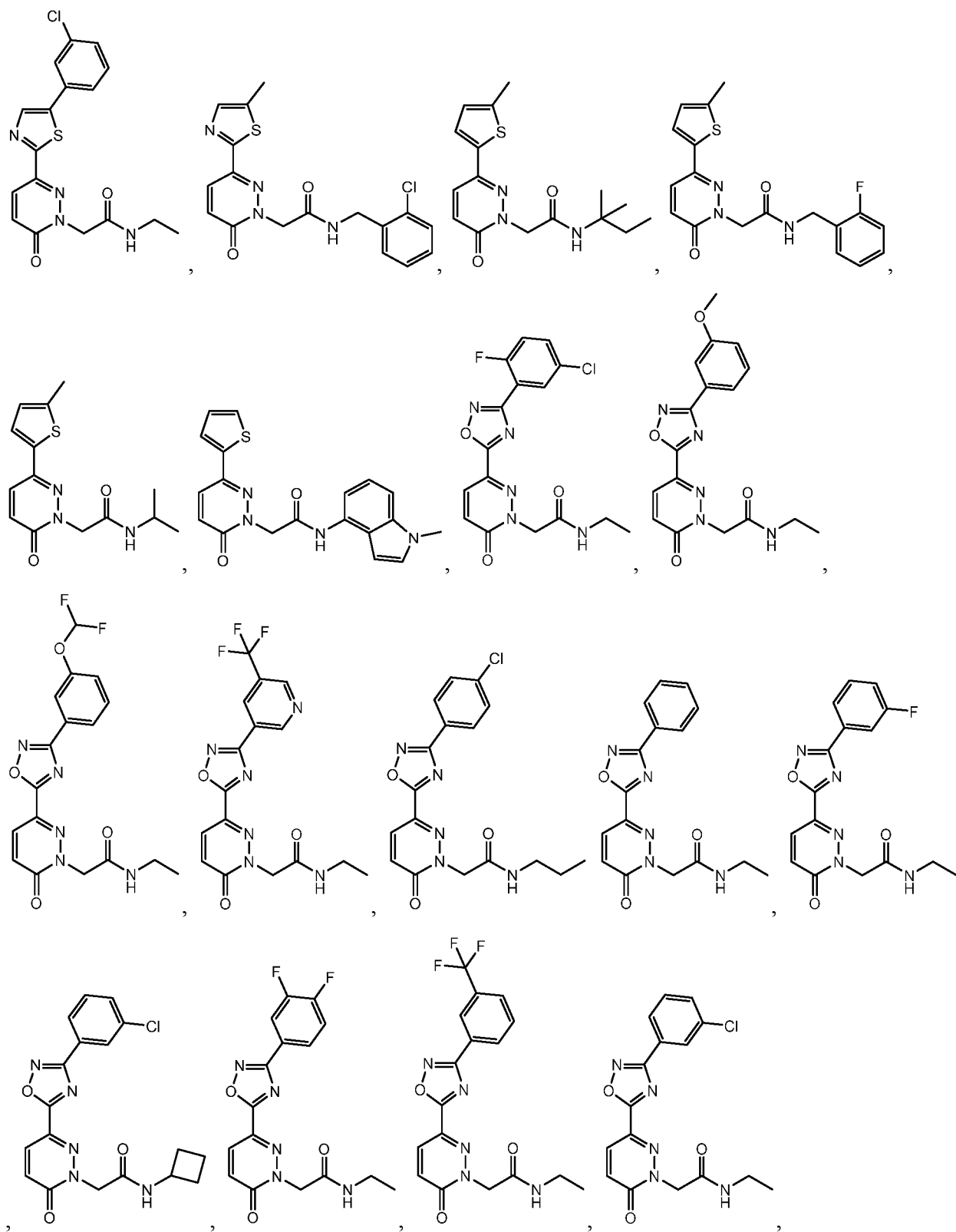




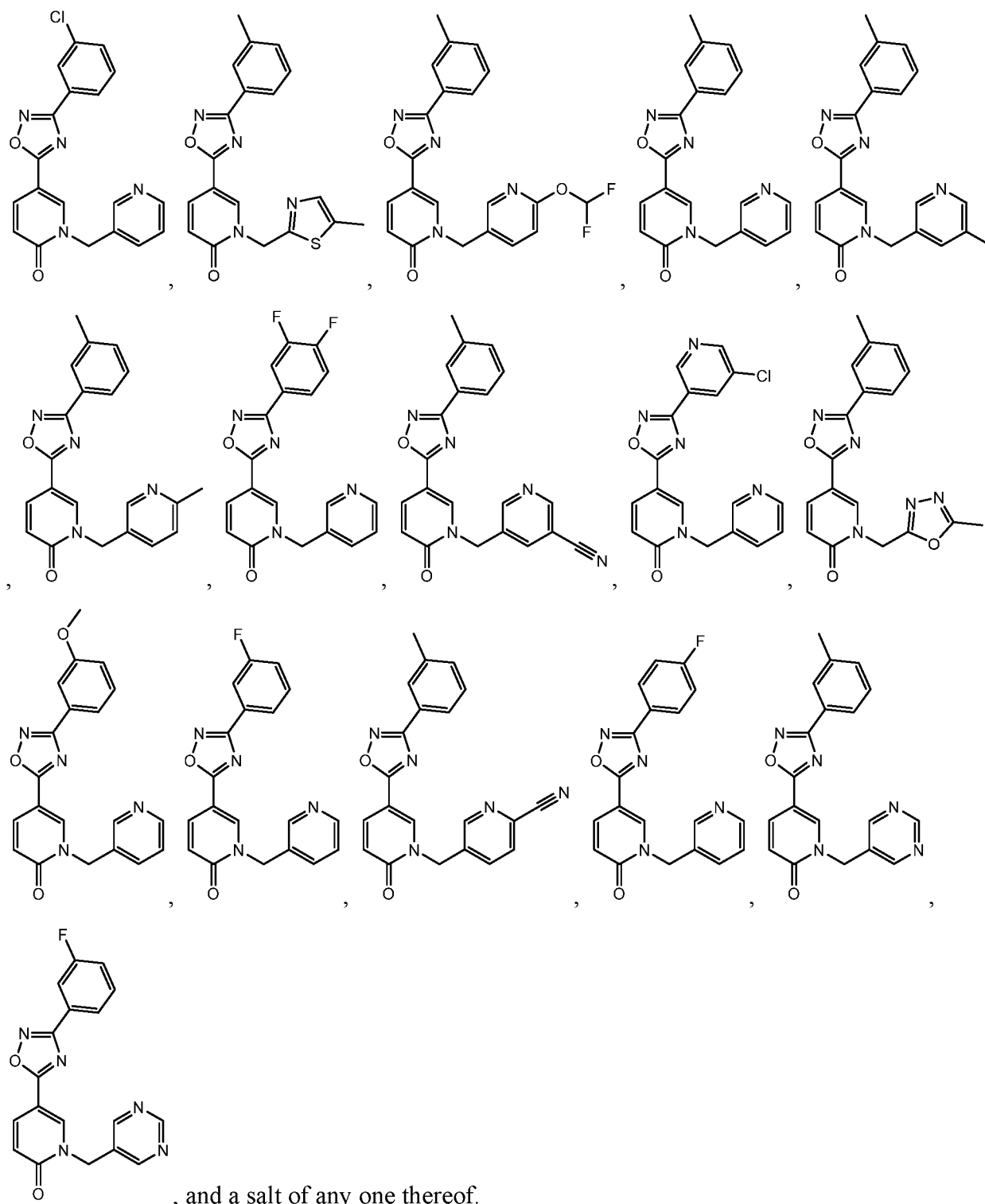
of any one thereof.

[0208] In certain embodiments, for a compound or salt of Formula (I) is selected from









[0209] Presented herein are methods to treat neuromuscular and movement disorders by reduction of skeletal muscle contraction. Treatment of subjects with neuromuscular and movement disorders with a selective fast skeletal muscle (type II) myosin inhibitor of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may reduce muscle breakdown by preventing excessive uncoordinated muscle contractures resulting in less muscle damage. Furthermore, methods of the disclosure may reduce muscle damage while minimizing the impact on physical function in subjects. Preservation of function may occur both by limiting damaging

levels of force generation in type II fibers and by increasing reliance on healthier type I fibers. Reduction of skeletal muscle contraction or uncoordinated muscle contractures can be reduced by the inhibition of skeletal myosin II. In certain embodiments, the inhibitor of skeletal myosin II is a compound or salt of Formula (I), (IIA), (IIB), or (IIC) as disclosed herein.

[0210] In some embodiments, disclosed herein is a method of inhibiting muscle myosin II, comprising administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to a subject in need thereof. In some embodiments, the compound or salt does not appreciably inhibit cardiac muscle contraction. In some embodiments, wherein the compound or salt does not appreciably inhibit cardiac muscle contraction. In some embodiments, the compound or salt reduces cardiac muscle force by less than 10%.

[0211] In some aspects, methods of treating neuromuscular conditions or movement disorders may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to inhibit skeletal muscle contraction. In some embodiments, the compound or salt of Formula (I), (IIA), (IIB), or (IIC) does not significantly inhibit cardiac muscle contraction. In some embodiments, cardiac muscle contraction is inhibited by 20% or less. In some embodiments, cardiac muscle contraction is inhibited by 15% or less. In some embodiments, cardiac muscle contraction is inhibited by 10% or less. In some embodiments, cardiac muscle contraction is inhibited by 9% or less. In some embodiments, cardiac muscle contraction is inhibited by 8% or less. In some embodiments, cardiac muscle contraction is inhibited by 7% or less. In some embodiments, cardiac muscle contraction is inhibited by 6% or less. In some embodiments, cardiac muscle contraction is inhibited by 5% or less. In some embodiments, cardiac muscle contraction is inhibited by 4% or less. In some embodiments, cardiac muscle contraction is inhibited by 3% or less. In some embodiments, cardiac muscle contraction is inhibited by 2% or less. In some embodiments, cardiac muscle contraction is inhibited by 1% or less.

[0212] A subject's activities of daily life (ADL) or habitual physical activity may be monitored prior to and following the treatment with a compound or salt of Formula (I), (IIA), (IIB), or (IIC). ADL or habitual physical activity is subject-dependent and may range from simple walking to extensive exercise depending on the subject's ability and routine. Treatment options and dosages of the skeletal muscle contraction inhibitors discussed herein may be personalized to a subject such that the ADL and habitual physical activity remains unchanged.

[0213] In some aspects, methods of treating neuromuscular conditions or movement disorders may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to inhibit skeletal muscle contraction. A compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be given in an amount relative to the amount needed to reduce skeletal muscle contraction by 50%.

The compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be administered in an amount less than the amount needed to reduce skeletal muscle contraction by 50% relative to pre-treatment skeletal muscle contraction capacity of the subject. The compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be administered in an amount that reduces skeletal muscle contraction by 5% to 45% relative to pre-treatment skeletal muscle contraction capacity of said subject. In some cases, the compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be administered in an amount that reduces skeletal muscle contraction by less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45% or even less than 50% relative to pre-treatment skeletal muscle contraction capacity of said subject. In certain embodiments, the compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be administered in an amount that reduces skeletal muscle contraction from 1% to 50% relative to pre-treatment skeletal muscle contraction capacity of said subject.

[0214] In some aspects, methods of treating neuromuscular conditions or movement disorders may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to inhibit type I skeletal muscle contraction. The inhibitor of type I skeletal muscle contraction may be given in an amount relative to the amount needed to reduce type I skeletal muscle contraction by 20%. The inhibitor of type I skeletal muscle contraction may be administered in an amount less than the amount needed to reduce type I skeletal muscle contraction by 20% relative to pre-treatment type I skeletal muscle contraction capacity of the subject. The inhibitor of type I skeletal muscle contraction may be administered in an amount that reduces type I skeletal muscle contraction by 0.01% to 20% relative to pre-treatment type I skeletal muscle contraction capacity of said subject. In some cases, the inhibitor may be administered in an amount that reduces type I skeletal muscle contraction by less than 0.01%, less than 0.1%, less than 0.5%, less than 1%, less than 5%, less than 10%, less than 15% or less than 20% relative to pre-treatment type I skeletal muscle contraction capacity of said subject. In certain embodiments, the inhibitor may be administered in an amount that reduces type I skeletal muscle contraction from 0.01% to 20% relative to pre-treatment type I skeletal muscle contraction capacity of said subject.

[0215] In some aspects, methods of treating neuromuscular conditions or movement disorders may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to inhibit type II skeletal muscle contraction. The inhibitor of type II skeletal muscle contraction may be given in an amount relative to the amount needed to reduce type II skeletal muscle contraction by 90%. The inhibitor of type II skeletal muscle contraction may be administered in an amount less than the amount needed to reduce type II skeletal muscle contraction by 90% relative to pre-treatment type II skeletal muscle contraction capacity of the subject. The inhibitor of type II

skeletal muscle contraction may be administered in an amount that reduces type II skeletal muscle contraction by 5% to 75% relative to pre-treatment type II skeletal muscle contraction capacity of said subject. In some cases, the inhibitor may be administered in an amount that reduces type II skeletal muscle contraction by less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%, less than 85% or even less than 90% relative to pre-treatment type II skeletal muscle contraction capacity of said subject. In certain embodiments, the inhibitor may be administered in an amount that reduces type II skeletal muscle contraction by from 1% to 50% relative to pre-treatment type II skeletal muscle contraction capacity of said subject.

[0216] In some aspects, methods of treating contraction-induced injury in skeletal muscle fiber may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to inhibit skeletal muscle contraction and/or skeletal muscle myosin II. In certain embodiments, the inhibitor does not appreciably inhibit cardiac muscle contraction.

[0217] In some aspects, methods of treating metabolic myopathies, e.g. McCardle's syndrome, may comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC).

[0218] In certain embodiments, the contraction-induced injury in skeletal muscle fiber is from involuntary skeletal muscle contraction. The involuntary skeletal muscle contraction may be associated with a neuromuscular condition or spasticity-associated condition. In certain embodiments, the contraction-induced injury in skeletal muscle fiber may be from voluntary skeletal muscle contraction, e.g., physical exercise.

[0219] In certain embodiments, the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to a subject modulates one or more biomarkers associated with muscle contraction. Examples of biomarkers include but are not limited to creatinine kinase (CK), Troponin T (TnT), Troponin C (TnC), Troponin I (TnI), pyruvate kinase (PK), lactate dehydrogenase (LDH), myoglobin, isoforms of TnI (such as cardiac, slow skeletal, fast skeletal muscles) and inflammatory markers (IL-1, IL-6, IL-4, TNF- α). Biomarkers may also include measures of muscle inflammation for example, edema. The level of biomarkers described herein may increase after the administration of the inhibitor relative to pre-treatment level of the biomarkers. Alternatively, the level of biomarkers may decrease after the administration of the inhibitor relative to pre-treatment level of the biomarkers. The modulation of one or more biomarkers with an inhibitor described herein may indicate treatment of a neuromuscular condition such as those described herein.

[0220] Levels of CK in a subject increase when the subject is active as compared to when the subject is inactive (e.g., sleeping) and therefore CK is a potential metric for evaluating skeletal muscle breakdown caused by skeletal muscle contraction. In certain embodiments, a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be administered to a subject prior to mild, moderate or strenuous activity to reduce or prevent skeletal muscle breakdown from the activity. Moderate to strenuous activity may be dependent on a subject's abilities and may include physical exercise that increases the heart rate by at least 20% or more, such as about 50% or more relative to the subject's resting heart rate. Examples of moderate to strenuous activity include walking, running, weight lifting, biking, swimming, hiking, etc.

[0221] In certain embodiments, a compound or salt of Formula (I), (IIA), (IIB), or (IIC) is administered prior to, during, or after moderate or strenuous activity to reduce or prevent skeletal muscle breakdown from the activity. The compound or salt of Formula (I), (IIA), (IIB), or (IIC) may reduce the subject's level of CK relative to the untreated subject performing the same activity. The level of CK may be measured in the peripheral blood of the subject during or after the activity. The administration of an inhibitor described herein may reduce the level of CK by 5% to 90% in an active subject relative to the untreated subject performing the same activity, thereby reducing or preventing skeletal muscle breakdown from the activity. The administration of an inhibitor described herein may modulate the level of CK by about 5% to about 90% relative to the untreated subject performing the same activity, thereby reducing or preventing skeletal muscle breakdown from the activity. The administration of an inhibitor described herein may reduce the level of CK by at least about 5% relative to the untreated subject performing the same activity thereby reducing or preventing skeletal muscle breakdown from the activity. The administration of an inhibitor described herein may modulate the level of CK by at most about 90% relative to the untreated subject performing the same activity. The administration of an inhibitor described herein may reduce the level of CK by about 5% to about 15%, about 5% to about 25%, about 5% to about 35%, about 5% to about 45%, about 5% to about 55%, about 5% to about 65%, about 5% to about 75%, about 5% to about 85%, about 5% to about 90%, about 15% to about 25%, about 15% to about 35%, about 15% to about 45%, about 15% to about 55%, about 15% to about 65%, about 15% to about 75%, about 15% to about 85%, about 15% to about 90%, about 25% to about 35%, about 25% to about 45%, about 25% to about 55%, about 25% to about 65%, about 25% to about 75%, about 25% to about 85%, about 25% to about 90%, about 35% to about 45%, about 35% to about 55%, about 35% to about 65%, about 35% to about 75%, about 35% to about 85%, about 35% to about 90%, about 45% to about 55%, about 45% to about 65%, about 45% to about 75%, about 45% to about 85%, about 45% to about 90%, about 55% to

about 65%, about 55% to about 75%, about 55% to about 85%, about 55% to about 90%, about 65% to about 75%, about 65% to about 85%, about 65% to about 90%, about 75% to about 85%, about 75% to about 90%, or about 85% to about 90% relative to the untreated subject performing the same activity, thereby reducing or preventing skeletal muscle breakdown from the activity. The administration of an inhibitor described herein may modulate the level of CK by about 5%, about 15%, about 25%, about 35%, about 45%, about 55%, about 65%, about 75%, about 85%, or about 90% relative to the untreated subject performing the same activity, thereby reducing or preventing skeletal muscle breakdown from the activity.

[0222] The administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to a subject may modulate the levels of inflammatory markers, e.g., reduce the level of one or more inflammatory markers relative to the untreated subject or the subject prior to treatment. The level of inflammatory markers may be measured in the peripheral blood of the subject. Examples of inflammatory markers may include but are not limited to IL-1, IL-6 and TNF- α . Inflammatory markers may also be in the form of conditions such as edema which may be measured using magnetic resonance imaging. The level of inflammatory markers in the peripheral blood may increase after the administration of the inhibitor relative to pre-treatment level of inflammatory marker for the subject. Alternatively, the level of inflammatory markers in the peripheral blood may decrease after the administration of the inhibitor relative to pre-treatment level of inflammatory marker for the subject. The administration of an inhibitor described herein may modulate the level of inflammatory markers by 5% to 90% relative to pre-treatment level of inflammatory marker for the subject. In some cases, the level of inflammatory markers may be modulated by about 5% to about 90% relative to pre-treatment level of inflammatory markers of the subject. In some cases, the level of inflammatory markers may be modulated by at least about 5% relative to pre-treatment level of inflammatory markers of the subject. In some cases, the level of inflammatory markers may be modulated by at most about 90% relative to pre-treatment level of inflammatory markers of the subject. In some cases, the level of inflammatory markers may be modulated by about 5% to about 15%, about 5% to about 25%, about 5% to about 35%, about 5% to about 45%, about 5% to about 55%, about 5% to about 65%, about 5% to about 75%, about 5% to about 85%, about 5% to about 90%, about 15% to about 25%, about 15% to about 35%, about 15% to about 45%, about 15% to about 55%, about 15% to about 65%, about 15% to about 75%, about 15% to about 85%, about 15% to about 90%, about 25% to about 35%, about 25% to about 45%, about 25% to about 55%, about 25% to about 65%, about 25% to about 75%, about 25% to about 85%, about 25% to about 90%, about 35% to about 45%, about 35% to about 55%, about 35% to about 65%, about 35% to about 75%, about 35% to about 85%, about

35% to about 90%, about 45% to about 55%, about 45% to about 65%, about 45% to about 75%, about 45% to about 85%, about 45% to about 90%, about 55% to about 65%, about 55% to about 75%, about 55% to about 85%, about 55% to about 90%, about 65% to about 75%, about 65% to about 85%, about 65% to about 90%, about 75% to about 85%, about 75% to about 90%, or about 85% to about 90% relative to pre-treatment level of inflammatory markers of the subject. In some cases, the level of inflammatory markers may be modulated by about 5%, about 15%, about 25%, about 35%, about 45%, about 55%, about 65%, about 75%, about 85%, or about 90% relative to pre-treatment level of inflammatory markers of the subject.

[0223] The administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) to a subject may modulate the levels of circulating fast skeletal muscle Troponin I (fS-TnI). The level of fS-TnI may be measured in the peripheral blood. The level of fS-TnI in the peripheral blood may increase after the administration of the inhibitor relative to pre-treatment level of fS-TnI for the subject. Alternatively, the level of fS-TnI in the peripheral blood may decrease after the administration of the inhibitor relative to pre-treatment level of fS-TnI for the subject. The administration of an inhibitor described herein may modulate the level of fS-TnI by 5% to 90% relative to pre-treatment level of fS-TnI for the subject. In some cases, the level of fS-TnI may be modulated by at least about 5% relative to pre-treatment level of fS-TnI of the subject. In some cases, the level of fS-TnI may be modulated by at most about 90% relative to pre-treatment level of fS-TnI of the subject. In some cases, the level of fS-TnI may be modulated by about 5% to about 15%, about 5% to about 25%, about 5% to about 35%, about 5% to about 45%, about 5% to about 55%, about 5% to about 65%, about 5% to about 75%, about 5% to about 85%, about 5% to about 90%, about 15% to about 25%, about 15% to about 35%, about 15% to about 45%, about 15% to about 55%, about 15% to about 65%, about 15% to about 75%, about 15% to about 85%, about 15% to about 90%, about 25% to about 35%, about 25% to about 45%, about 25% to about 55%, about 25% to about 65%, about 25% to about 75%, about 25% to about 85%, about 25% to about 90%, about 35% to about 45%, about 35% to about 55%, about 35% to about 65%, about 35% to about 75%, about 35% to about 85%, about 35% to about 90%, about 45% to about 55%, about 45% to about 65%, about 45% to about 75%, about 45% to about 85%, about 45% to about 90%, about 55% to about 65%, about 55% to about 75%, about 55% to about 85%, about 55% to about 90%, about 65% to about 75%, about 65% to about 85%, about 65% to about 90%, about 75% to about 85%, about 75% to about 90%, or about 85% to about 90% relative to pre-treatment level of fS-TnI of the subject. In some cases, the level of fS-TnI may be modulated by about 5%, about 15%, about 25%, about 35%, about 45%, about 55%, about 65%, about 75%, about 85%, or about 90% relative to pre-treatment level of fS-TnI of the subject.

[0224] Isoforms of troponin may be measured in a subject prior to and following the administration a compound or salt of Formula (I), (IIA), (IIB), or (IIC). Inhibition of skeletal muscle contraction may not inhibit some isoforms of troponin, such as cardiac troponin I (cTnI) or slow skeletal troponin I (ssTnI). In some cases, the inhibition of skeletal muscle contraction may not appreciably inhibit cTnI or ssTnI. As used herein with regard to cTnI or ssTnI, the phrase not appreciably refers to the cTnI or ssTnI reduced by less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or even less than 0.1% relative to the cTnI or ssTnI prior to the administration of the inhibitor.

[0225] The administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may reduce involuntary muscle contractions. Involuntary muscle contractions may be reduced by 20% to 90% relative to involuntary muscle contractions prior to the administration of the inhibitor. In some cases, involuntary muscle contractions may be reduced by at least about 20% relative to pre-treatment involuntary muscle contractions. In some cases, involuntary muscle contractions may be reduced by at most about 90% relative to pre-treatment involuntary muscle contractions. In some cases, involuntary muscle contractions may be reduced by about 20% to about 25%, about 20% to about 30%, about 20% to about 40%, about 20% to about 50%, about 20% to about 70%, about 20% to about 75%, about 20% to about 80%, about 20% to about 85%, about 20% to about 90%, about 25% to about 30%, about 25% to about 40%, about 25% to about 50%, about 25% to about 70%, about 25% to about 75%, about 25% to about 80%, about 25% to about 85%, about 25% to about 90%, about 30% to about 40%, about 30% to about 50%, about 30% to about 70%, about 30% to about 75%, about 30% to about 80%, about 30% to about 85%, about 30% to about 90%, about 40% to about 50%, about 40% to about 70%, about 40% to about 75%, about 40% to about 80%, about 40% to about 85%, about 40% to about 90%, about 50% to about 70%, about 50% to about 75%, about 50% to about 80%, about 50% to about 85%, about 50% to about 90%, about 70% to about 75%, about 70% to about 80%, about 70% to about 85%, about 70% to about 90%, about 75% to about 80%, about 75% to about 85%, about 75% to about 90%, about 80% to about 85%, about 80% to about 90%, or about 85% to about 90% relative to pre-treatment involuntary muscle contractions. In some cases, involuntary muscle contractions may be reduced by about 20%, about 25%, about 30%, about 40%, about 50%, about 70%, about 75%, about 80%, about 85%, or about 90% relative to pre-treatment involuntary muscle contractions.

[0226] A compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be used to improve activities of daily living (ADL) or habitual physical activity in a subject as mature, functional undamaged muscle may be restored. Examples of ADL or habitual activities include but are not

limited to stair climb, time to get up, timed chair rise, habitual walk speed, North Star Ambulatory assessment, incremental/endurance shuttle walk and 6 minute walk distance tests. ADL or habitual physical activity levels or capacity may be measured prior to and following the administration of a skeletal muscle inhibitor. Inhibition of skeletal muscle contraction may not affect ADL or habitual physical activity. In some cases, the inhibition of skeletal muscle contraction may not appreciably affect ADL or habitual physical activity. As used herein with regard to ADL or habitual physical activity, the phrase not appreciably refers to the level of ADL or habitual activity reduced by less than 20%, less than 15%, less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or even less than 0.1% relative to the ADL or habitual activity prior to the administration of the inhibitor. Skeletal muscle contraction or force in a subject may be measured prior to and following the administration of the compound or salt of Formula (I), (IIA), (IIB), or (IIC). Such measurements may be performed to generate a dose response curve for the compound or salt of Formula (I), (IIA), (IIB), or (IIC). Dosage of the compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be adjusted by about 5% to 50% relative to a dose that reduces type II skeletal muscle contraction by 90%. In some cases, dosage of the skeletal muscle contraction inhibitor may be adjusted by at least about 5% relative to a dose that reduces type II skeletal muscle contraction by 90%. In some cases, dosage of the skeletal muscle contraction inhibitor may be adjusted by at most about 50% relative to a dose that reduces type II skeletal muscle contraction by 90%. In some cases, dosage of the skeletal muscle contraction inhibitor may be adjusted by about 5 % to about 10 %, about 5 % to about 15 %, about 5 % to about 20 %, about 5 % to about 25 %, about 5 % to about 30 %, about 5 % to about 35 %, about 5 % to about 40 %, about 5 % to about 50 %, about 10 % to about 15 %, about 10 % to about 20 %, about 10 % to about 25 %, about 10 % to about 30 %, about 10 % to about 35 %, about 10 % to about 40 %, about 10 % to about 50 %, about 15 % to about 20 %, about 15 % to about 25 %, about 15 % to about 30 %, about 15 % to about 35 %, about 15 % to about 40 %, about 15 % to about 50 %, about 20 % to about 25 %, about 20 % to about 30 %, about 20 % to about 35 %, about 20 % to about 40 %, about 20 % to about 50 %, about 25 % to about 30 %, about 25 % to about 35 %, about 25 % to about 40 %, about 25 % to about 50 %, about 30 % to about 35 %, about 30 % to about 40 %, about 30 % to about 50 %, about 35 % to about 40 %, about 35 % to about 50 %, or about 40 % to about 50 % relative to a dose that reduces type II skeletal muscle contraction by 90%. In some cases, dosage of the skeletal muscle contraction inhibitor may be adjusted by about 10%, about 12%, about 15%, about 18%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% relative to a dose that reduces type II skeletal muscle contraction by 90%. Skeletal muscle

contraction may be measured by a muscle force test after nerve stimulation using surface electrodes (e.g., foot plantar flexion after peroneal nerve stimulation in the leg), isolated limb assay, heart rate monitor or an activity monitor or equivalents thereof prior to and following the administration of a skeletal muscle contraction inhibitor.

[0227] Cardiac muscle force or cardiac muscle contraction of a subject may be measured prior to and following the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC).

Inhibition of skeletal muscle contraction may not inhibit cardiac muscle contraction or cardiac muscle force. In some embodiments, the inhibition of skeletal muscle contraction may not appreciably inhibit cardiac muscle contraction. In certain embodiments with regard to cardiac muscle contraction, the phrase not appreciably refers to cardiac muscle force reduced by less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or even less than 0.1% relative to the cardiac muscle force prior to the administration of the inhibitor. Cardiac muscle force or cardiac muscle contraction of a subject following the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be within 0.1% to 10% of the cardiac muscle contraction or cardiac muscle force prior to the administration of the inhibitor. In some embodiments, administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may inhibit skeletal muscle contraction and cardiac muscle contraction or cardiac muscle force. In some embodiments, cardiac muscle force reduced by more than 0.1%, more than 0.5%, more than 1%, more than 2%, more than 4%, more than 6%, more than 8%, or more than 10%. In some embodiments, a reduction of skeletal muscle contraction and cardiac muscle contraction are described by a ratio to one another. For example, in some embodiments, the ratio of the reduction in skeletal muscle contraction to reduction in cardiac muscle contraction is from about 1:1 to about 100:1, about 2:1 to about 50:1, about 3:1 to about 40:1, about 4:1 to about 30:1, about 5:1 to about 20:1, about 7:1 to about 15:1, or about 8:1 to about 12:1. Cardiac muscle force or cardiac muscle contraction may be measured using an echocardiogram (fractional shortening) or other equivalent tests.

[0228] Tidal volume in lung in a subject may be measured prior to and following the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC). Administration may not inhibit tidal volume in a lung. In some cases, administration may not appreciably inhibit tidal volume in a lung. In certain embodiments with regard to tidal lung volume in a lung, the phrase not appreciably refers to the tidal volume in a lung reduced by less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or less than 0.1% relative to the tidal volume in a lung prior to the administration of the inhibitor. Tidal volume in a lung in a

subject may be measured using forced volume in one second test (FEV1) or forced vital capacity test (FVC) or equivalent tests thereof.

[0229] Smooth muscle contraction in a subject may be measured prior to and following the administration of a skeletal muscle contraction inhibitor. Inhibition of skeletal muscle contraction may not inhibit smooth muscle contraction. In some cases, the inhibition of skeletal muscle contraction may not appreciably inhibit smooth muscle contraction. As used herein with regard to smooth muscle contraction, the phrase not appreciably refers to the smooth muscle contraction reduced by less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or even less than 0.1% relative to the smooth muscle contraction prior to the administration of the inhibitor. Smooth muscle contraction in a subject may be evaluated by measuring a subject's blood pressure.

[0230] Neuromuscular coupling in a subject may be measured prior to and following the administration of a compound or salt of Formula (I), (IIA), (IIB), or (IIC). Inhibition of skeletal muscle contraction, with an inhibitor described herein, may not impair nerve conduction, neurotransmitter release or electrical depolarization of skeletal muscle in a subject. In some cases, the inhibition of skeletal muscle contraction may not appreciably impair neuromuscular coupling in a subject. As used herein with regard to neuromuscular coupling, the phrase not appreciably refers to a level of neuromuscular coupling in the subject reduced by less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or less than 0.1% relative to the level of neuromuscular coupling in the subject prior to the administration of the inhibitor. Neuromuscular coupling in a subject may be evaluated by measuring nerve induced electrical depolarization of skeletal muscle by the recording of electrical activity produced by skeletal muscles after electrical or voluntary stimulation with electromyography (EMG) using surface or needle electrodes .

[0231] In some aspects, the method of treating a neuromuscular condition or movement disorder can comprise administering a compound or salt of Formula (I), (IIA), (IIB), or (IIC) wherein the compound or salt of Formula (I), (IIA), (IIB), or (IIC) may inhibit myosin ATPase activity, native skeletal muscle myofibril ATPase (calcium regulated) or a reconstituted S1 with actin, tropomyosin and troponin. *In vitro* assays may be used to test the effect of the test compound or inhibitor on the myosin ATPase activity. Test compounds can be screened for assessing their inhibitory activity of muscle contraction. Inhibitory activity can be measured using an absorbance assay to determine actin-activated ATPase activity. Rabbit muscle myosin sub-fragment 1 (S1) can be mixed with polymerized actin and distributed into wells of assay plates without nucleotides. Test compounds can then be added into the wells with a pin array. The

reaction can be initiated with MgATP. The amount of ATP consumption over a defined time period in the test vessel may be compared to the amount of ATP consumption in a control vessel. The defined period of time may be 5 minutes to 20 minutes. The ATP consumption can be determined by direct or indirect assays. The test compounds that reproducibly and strongly inhibited the myosin S1 ATPase activity can be evaluated further in dose response assay to determine IC₅₀ for the compound *ex vivo* on dissected muscles. The assay may measure ATPase activity indirectly by coupling the myosin to pyruvate kinase and lactate dehydrogenase to provide an absorbance detection method at 340nm based upon the conversion of NADH to NAD⁺ driven by ADP accumulation. In some cases, wherein ATP consumption is decreased by at least 20% in said test vessel than said control vessel, said test compound may be selected as a compound or salt of Formula (I), (IIA), (IIB), or (IIC). A test compound may be selected when there is at least 20% greater inhibition of NAD⁺ generation in a kinetic assay.

[0232] The inhibitor or test compound selected may not inhibit cardiac muscle myosin S1 ATPase in *in vitro* assays. In some cases, the cardiac muscle myosin S1 ATPase or cardiac myofibrils or reconstituted system may be inhibited by less than 10%, less than 8%, less than 5%, less than 3%, less than 2%, less than 1% or less than 0.5% when a test compound or compound or salt of Formula (I), (IIA), (IIB), or (IIC) is tested in an *in-vitro* assay.

[0233] Test compounds of skeletal muscle contraction may be tested on skinned fibers. Single skeletal muscle fibers, treated so as to remove membranes and allow for a direct activation of contraction after calcium administration may be used. An inhibitor compound or salt of Formula (I), (IIA), (IIB), or (IIC) may inhibit contraction of a single skeletal muscle fiber by about 5 % to about 90 % relative to pre-treatment value or an untreated control single skeletal muscle fiber. An inhibitor may inhibit contraction of a single skeletal muscle fiber by at least about 5 % relative to pre-treatment value or an untreated control single skeletal muscle fiber. An inhibitor may inhibit contraction of a single skeletal muscle fiber by at most about 90 % relative to pre-treatment value or an untreated control single skeletal muscle fiber. An inhibitor may inhibit contraction of a single skeletal muscle fiber by about 5 % to about 10 %, about 5 % to about 20 %, about 5 % to about 30 %, about 5 % to about 40 %, about 5 % to about 50 %, about 5 % to about 60 %, about 5 % to about 70 %, about 5 % to about 80 %, about 5 % to about 90 %, about 10 % to about 20 %, about 10 % to about 30 %, about 10 % to about 40 %, about 10 % to about 50 %, about 10 % to about 60 %, about 10 % to about 70 %, about 10 % to about 80 %, about 10 % to about 90 %, about 20 % to about 30 %, about 20 % to about 40 %, about 20 % to about 50 %, about 20 % to about 60 %, about 20 % to about 70 %, about 20 % to about 80 %, about 20 % to about 90 %, about 30 % to about 40 %, about 30 % to about 50 %, about 30 % to about 60 %, about 30 % to about 70 %, about 30 % to about 80 %, about 30 % to about 90 %, about 40 % to about 50 %, about 40 % to about 60 %, about 40 % to about 70 %, about 40 % to about 80 %, about 40 % to about 90 %, about 50 % to about 60 %, about 50 % to about 70 %, about 50 % to about 80 %, about 50 % to about 90 %, about 60 % to about 70 %, about 60 % to about 80 %, about 60 % to about 90 %, about 70 % to about 80 %, about 70 % to about 90 %, about 80 % to about 90 %.

about 30 % to about 70 %, about 30 % to about 80 %, about 30 % to about 90 %, about 40 % to about 50 %, about 40 % to about 60 %, about 40 % to about 70 %, about 40 % to about 80 %, about 40 % to about 90 %, about 50 % to about 60 %, about 50 % to about 70 %, about 50 % to about 80 %, about 50 % to about 90 %, about 60 % to about 70 %, about 60 % to about 80 %, about 60 % to about 90 %, about 70 % to about 80 %, about 70 % to about 90 %, or about 80 % to about 90 % relative to pre-treatment capacity or an untreated control single skeletal muscle fiber. An inhibitor may inhibit contraction of a single skeletal muscle fiber by about 5 %, about 10 %, about 20 %, about 30 %, about 40 %, about 50 %, about 60 %, about 70 %, about 80 %, or about 90 % relative to pre-treatment capacity or an untreated control single skeletal muscle fiber.

[0234] An inhibitor compound or salt of Formula (I), (IIA), (IIB), or (IIC) may inhibit contraction of a single skeletal muscle by about 5 % to about 90 % relative to pre-treatment value or an untreated control single skeletal muscle. An inhibitor may inhibit contraction of a single skeletal muscle by at least about 5 % relative to pre-treatment value or an untreated control single skeletal muscle. An inhibitor may inhibit contraction of a single skeletal muscle by at most about 90 % relative to pre-treatment value or an untreated control single skeletal muscle. An inhibitor may inhibit contraction of a single skeletal muscle by about 5 % to about 10 %, about 5 % to about 20 %, about 5 % to about 30 %, about 5 % to about 40 %, about 5 % to about 50 %, about 5 % to about 60 %, about 5 % to about 70 %, about 5 % to about 80 %, about 5 % to about 90 %, about 10 % to about 20 %, about 10 % to about 30 %, about 10 % to about 40 %, about 10 % to about 50 %, about 10 % to about 60 %, about 10 % to about 70 %, about 10 % to about 80 %, about 10 % to about 90 %, about 20 % to about 30 %, about 20 % to about 40 %, about 20 % to about 50 %, about 20 % to about 60 %, about 20 % to about 70 %, about 20 % to about 80 %, about 20 % to about 90 %, about 30 % to about 40 %, about 30 % to about 50 %, about 30 % to about 60 %, about 30 % to about 70 %, about 30 % to about 80 %, about 30 % to about 90 %, about 40 % to about 50 %, about 40 % to about 60 %, about 40 % to about 70 %, about 40 % to about 80 %, about 40 % to about 90 %, about 50 % to about 60 %, about 50 % to about 70 %, about 50 % to about 80 %, about 50 % to about 90 %, about 60 % to about 70 %, about 60 % to about 80 %, about 60 % to about 90 %, about 70 % to about 80 %, about 70 % to about 90 %, or about 80 % to about 90 % relative to pre-treatment capacity or an untreated control single skeletal muscle. An inhibitor may inhibit contraction of a single skeletal muscle by about 5 %, about 10 %, about 20 %, about 30 %, about 40 %, about 50 %, about 60 %, about 70 %, about 80 %, or about 90 % relative to pre-treatment capacity or an untreated control single skeletal muscle.

[0235] The effect of a test compound on slow type I skeletal muscle fibers, cardiac muscle bundles or lung muscle fibers, may be evaluated. A test compound or inhibitor compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be selected so as not to appreciably modulate the function of slow type I skeletal muscle fibers, cardiac muscle bundles or lung muscle fibers and be specific for type II skeletal muscles. As used herein, the term “appreciably modulate” can refer to the contraction capacity of muscles following the inhibitor administration to be reduced less than 10%, less than 8%, less than 6%, less than 4%, less than 2%, less than 1%, less than 0.5% or even less than 0.1% relative to the muscle force/contraction prior to the administration of the inhibitor.

[0236] In some aspects, a method of treating a neuromuscular condition or a movement disorder may comprise administering to a subject in need thereof a compound or salt of Formula (I), (IIA), (IIB), or (IIC) wherein the compound or salt of Formula (I), (IIA), (IIB), or (IIC) reduces skeletal muscle contraction by 5% to 90% in an *ex vivo* assay. The *ex vivo* assays used may be mouse models. The mouse models used may be dystrophy mouse models such as an mdx mouse. The mdx mouse has a point mutation in its dystrophin gene, changing the amino acid coding for a glutamine to a threonine producing a nonfunctional dystrophin protein resulting in DMD where there is increased muscle damage and weakness. Extensor digitorum longus muscles may be dissected from mdx mice and mounted on a lever arm. The muscles may be bathed in an oxygenated Krebs solution to maintain muscle function. A test compound or compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be applied to the muscles. An isometric (fixed length) contraction step may then be performed wherein the muscles are stimulated with a series of electrical pulses. An eccentric (lengthening) contraction step may be performed wherein the muscles are stretched to 10%, 15%, 20%, 25%, or 30% greater than its rested length, while relaxed or while stimulated with an electrical pulse. In some embodiments, the eccentric contraction step is repeated from 2 to 50 times. In some embodiments, the eccentric contraction step is repeated from 2 to 40 times. In some embodiments, the eccentric contraction step is repeated from 2 to 30 times. In some embodiments, the eccentric contraction step is repeated from 2 to 20 times. In some embodiments, the eccentric contraction step is repeated from 2 to 10 times. In some embodiments, the eccentric contraction step is repeated 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 times to cause muscle fiber injury. In some embodiments, the electric pulses may have a frequency of about 1 Hz to about 500 Hz. In some embodiments, the electric pulses may have a frequency of about 1 Hz to about 400 Hz. In some embodiments, the electric pulses may have a frequency of about 1 Hz to about 300 Hz. In some embodiments, the electric pulses may have a frequency of about 1 Hz to about 200 Hz. In some embodiments, the electric pulses may

have a frequency of about 1 Hz to about 100 Hz. The electric pulse may have a frequency of about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145 or 150 Hz. A series of electric pulses may comprise of individual pulses of different frequencies. The time period of each pulse in the series of electric pulses may be between 0.1 second to 0.5 seconds for each pulse. The time for each pulse may be 0.1, 0.2, 0.3, 0.35, 0.4 or 0.5 seconds. Muscle membrane damage may also be measured by incubating muscles in procion orange after the isometric or eccentric contraction. Procion orange is a fluorescent dye that is taken up by muscle fibers with injured membranes. The number or proportion of dye-positive fibers may then quantified by histology. When the test force drop and/or proportion of dye-positive fibers may be at least 20% less than the control force drop and/or dye uptake, the test compound may be selected as a compound or salt of Formula (I), (IIA), (IIB), or (IIC).

[0237] Using an isometric or eccentric set of contractions, the force generated by the muscle may be measured. The change in force generated by the muscle before and after an isometric or eccentric set of contractions may be calculated as the test force drop. The calculations may be compared to the change in force generated by the muscle contraction from the first pulse to the last pulse in a control sample without exposure to the test compound (control force drop). Force drop can be used as a surrogate of muscle injury and a test compound or inhibitor compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be selected when the test force drop is at least 20% less than the control force drop.

Pharmaceutical Formulations

[0238] The compositions and methods described herein may be considered useful as pharmaceutical compositions for administration to a subject in need thereof. Pharmaceutical compositions may comprise a compound or salt of Formula (I), (IIA), (IIB), or (IIC) described herein and one or more pharmaceutically acceptable carriers, diluents, excipients, stabilizers, dispersing agents, suspending agents, and/or thickening agents.

[0239] Pharmaceutical compositions comprising a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries. Formulation may be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a compound, salt or conjugate may be manufactured, for example, by lyophilizing the compound, salt or conjugate, mixing, dissolving, emulsifying, encapsulating or entrapping the conjugate. The pharmaceutical compositions may also include the compounds, salts or conjugates in a free-base form or pharmaceutically-acceptable salt form.

[0240] Methods for formulation of a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may include formulating any of the compounds, salts or conjugates with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions may include, for example, powders, tablets, dispersible granules and capsules, and in some aspects, the solid compositions further contain nontoxic, auxiliary substances, for example wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives. Alternatively, the compounds, salts or conjugates may be lyophilized or in powder form for re-constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0241] Pharmaceutical compositions comprising a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may comprise at least one active ingredient (e.g., a compound, salt or conjugate and other agents). The active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (e.g., hydroxymethylcellulose or gelatin microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug-delivery systems (e.g., liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions.

[0242] The compositions and formulations may be sterilized. Sterilization may be accomplished by filtration through sterile filtration.

[0243] The compositions comprising a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be formulated for administration as an injection. Non-limiting examples of formulations for injection may include a sterile suspension, solution or emulsion in oily or aqueous vehicles. Suitable oily vehicles may include, but are not limited to, lipophilic solvents or vehicles such as fatty oils or synthetic fatty acid esters, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension. The suspension may also contain suitable stabilizers. Injections may be formulated for bolus injection or continuous infusion. Alternatively, the compositions may be lyophilized or in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0244] For parenteral administration, a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable parenteral vehicle. Such vehicles may be inherently non-toxic, and non-therapeutic. Vehicles may be water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Non-aqueous vehicles such as fixed oils and ethyl oleate may also be used. Liposomes may be used as carriers. The vehicle may contain

minor amounts of additives such as substances that enhance isotonicity and chemical stability (e.g., buffers and preservatives).

[0245] In one embodiment the invention relates to methods and compositions of Formula (I), (IIA), (IIB), or (IIC) formulated for oral delivery to a subject in need. In one embodiment a composition is formulated so as to deliver one or more pharmaceutically active agents to a subject through a mucosa layer in the mouth or esophagus. In another embodiment the composition is formulated to deliver one or more pharmaceutically active agents to a subject through a mucosa layer in the stomach and/or intestines.

[0246] In one embodiment compositions of Formula (I), (IIA), (IIB), or (IIC) are provided in modified release dosage forms. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multi-particulate devices, and combinations thereof. The compositions may also comprise non-release controlling excipients.

[0247] In another embodiment compositions of Formula (I), (IIA), (IIB), or (IIC) are provided in enteric coated dosage forms. These enteric coated dosage forms can also comprise non-release controlling excipients. In one embodiment the compositions are in the form of enteric-coated granules, as controlled-release capsules for oral administration. The compositions can further comprise cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, pyridazine, lactose, mannitol, or sodium lauryl sulfate. In another embodiment the compositions are in the form of enteric-coated pellets, as controlled-release capsules for oral administration. The compositions can further comprise glycerol monostearate 40-50, hydroxypropyl cellulose, pyridazine, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, or triethyl citrate.

[0248] In another embodiment the compositions of Formula (I), (IIA), (IIB), or (IIC) are enteric-coated controlled-release tablets for oral administration. The compositions can further comprise carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, pyridazine phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, or yellow ferric oxide.

[0249] Sustained-release preparations comprising a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be also be prepared. Examples of sustained-release preparations may include semipermeable matrices of solid hydrophobic polymers that may contain the compound, salt or conjugate, and these matrices may be in the form of shaped articles (e.g., films or microcapsules). Examples of sustained-release matrices may include polyesters, hydrogels (e.g., poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides, copolymers of L-

glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTM (i.e., injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

[0250] Pharmaceutical formulations comprising a compound or salt of Formula (I), (IIA), (IIB), or (IIC) may be prepared for storage by mixing a compound, salt or conjugate with a pharmaceutically acceptable carrier, excipient, and/or a stabilizer. This formulation may be a lyophilized formulation or an aqueous solution. Acceptable carriers, excipients, and/or stabilizers may be nontoxic to recipients at the dosages and concentrations used. Acceptable carriers, excipients, and/or stabilizers may include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives, polypeptides; proteins, such as serum albumin or gelatin; hydrophilic polymers; amino acids; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes; and/or non-ionic surfactants or polyethylene glycol.

[0251] In another embodiment the compositions of Formula (I), (IIA), (IIB), or (IIC) can further comprise calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

[0252] In another embodiment compositions of Formula (I), (IIA), (IIB), or (IIC) are provided in effervescent dosage forms. These effervescent dosage forms can also comprise non-release controlling excipients.

[0253] In another embodiment compositions of Formula (I), (IIA), (IIB), or (IIC) can be provided in a dosage form that has at least one component that can facilitate the immediate release of an active agent, and at least one component that can facilitate the controlled release of an active agent. In a further embodiment the dosage form can be capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The compositions can comprise one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances.

[0254] In another embodiment compositions of Formula (I), (IIA), (IIB), or (IIC) are provided in a dosage form for oral administration to a subject, which comprise one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric

juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[0255] In some embodiments, the compositions of Formula (I), (IIA), (IIB), or (IIC) provided herein can be in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human or non-human animal subjects and packaged individually. Each unit-dose can contain a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include, but are not limited to, ampoules, syringes, and individually packaged tablets and capsules. In some embodiments, unit-dosage forms may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container, which can be administered in segregated unit-dosage form. Examples of multiple-dosage forms include, but are not limited to, vials, bottles of tablets or capsules, or bottles of pints or gallons. In another embodiment the multiple dosage forms comprise different pharmaceutically active agents.

[0256] In some embodiments, the compositions of Formula (I), (IIA), (IIB), or (IIC) may also be formulated as a modified release dosage form, including immediate-, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, extended, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to known methods and techniques (see, Remington: The Science and Practice of Pharmacy, supra; Modified-Release Drug Delivery Technology, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, N.Y., 2002; Vol. 126, which are herein incorporated by reference in their entirety).

Combination Therapies

[0257] Also contemplated herein are combination therapies, for example, co-administering a disclosed compound and an additional active agent, as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually hours, days, weeks, months or years depending upon the combination selected). Combination therapy is intended to embrace administration of multiple therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered

at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

[0258] Substantially simultaneous administration is accomplished, for example, by administering to the subject a single formulation or composition, (e.g., a tablet or capsule having a fixed ratio of each therapeutic agent or in multiple, single formulations (e.g., capsules) for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent is effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents are administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected is administered by intravenous injection while the other therapeutic agents of the combination are administered orally. Alternatively, for example, all therapeutic agents are administered orally or all therapeutic agents are administered by intravenous injection.

[0259] The components of the combination are administered to a patient simultaneously or sequentially. It will be appreciated that the components are present in the same pharmaceutically acceptable carrier and, therefore, are administered simultaneously. Alternatively, the active ingredients are present in separate pharmaceutical carriers, such as, conventional oral dosage forms, that are administered either simultaneously or sequentially.

[0260] In certain embodiments, a compound or salt of the disclosure may be administered in combination with an oral corticosteroid. In certain embodiments, a compound or salt of the disclosure is administered in combination with deflazacort. In certain embodiments, a compound or salt of the disclosure is administered in combination with prednisone. In certain embodiments, a compound or salt of the disclosure is administered in combination with a morpholino antisense oligomer. In certain embodiments, a compound or salt of the disclosure is administered in combination with and exon skipping therapy. In certain embodiments, the additional therapeutic agent is eteplirsen or ataluren.

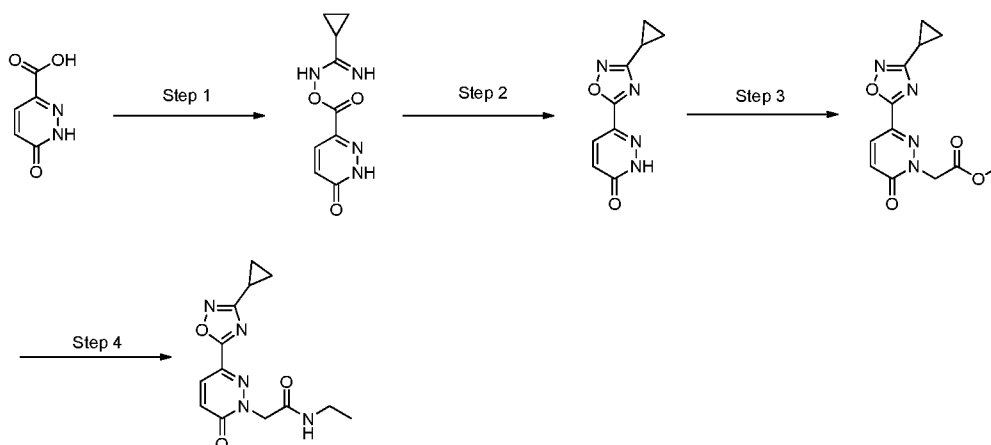
[0261] In certain embodiments, a compound or salt of the disclosure is used in combination with a gene therapy. In certain embodiments, the compound or salt of the disclosure is used in combination with adeno-associated virus (AAV) containing genes encoding replacement proteins, e.g., dystrophin, or truncated version thereof, e.g., microdystrophin. In certain embodiments, a compound or salt of the disclosure is administered in combination with vamorolone.

EXAMPLES

[0262] The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

[0263] The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein.

Example 1: 2-[3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-oxo-1,6-dihydropyridazin-1-yl]-N-ethylacetamide (Compound 15)



Step 1: 6-oxo-1,6-dihydropyridazine-3-carboxylate

[0264] To a stirred solution of 6-oxo-1,6-dihydropyridazine-3-carboxylic acid (200 mg, 1.43 mmol) in DCM (10 mL) were added N-hydroxycyclopropanecarboximidamide (157.22 mg, 1.57 mmol), DIC (270.24 mg, 2.14 mmol) and HOBt (289.35 mg, 2.14 mmol). The resulting mixture was stirred for 2 h at room temperature. The precipitated solids were collected by filtration and washed with THF (3 x 3 mL). The resulting solid was dried under vacuum to give the title compound as a white solid (290 mg, 91.42%) MS *m/z*: 223 [M+H]⁺.

Step 2: 6-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydropyridazin-3-one

[0265] A solution of 6-oxo-1,6-dihydropyridazine-3-carboxylate (290 mg, 1.31 mmol) in pyridine (3 mL) was stirred overnight at 103 °C. The reaction was quenched by the addition of

saturated aqueous NH_4Cl solution (5 mL), then diluted by water (20 mL) and extracted by EA (25 mL) twice. The combined EA phase was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude product. The crude product was purified by reversed phase Combi-flash chromatography to give the title compound as a yellow solid (220 mg, 82.3%) MS m/z : 205 $[\text{M}+\text{H}]^+$.

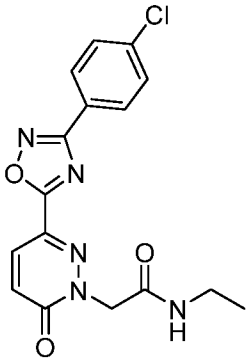
Step 3: methyl 2-[3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-oxo-1,6-dihydropyridazin-1-yl]acetate

[0266] To a stirred solution of 6-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydropyridazin-3-one (205 mg, 1.00 mmol) in DMF (5 mL) were added Cs_2CO_3 (654.23 mg, 2.00 mmol) and methyl 2-bromoacetate (153.58 mg, 1.00 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-TLC to give the title compound as a white solid (150 mg, 54.08%) MS m/z : 277 $[\text{M}+\text{H}]^+$.

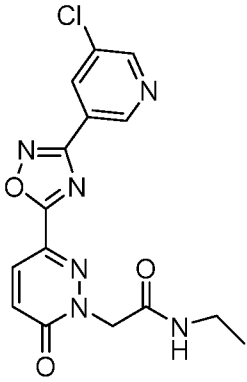
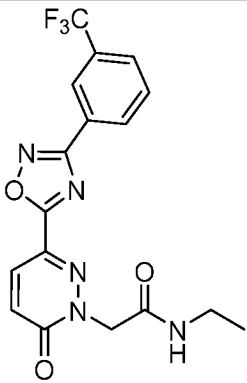
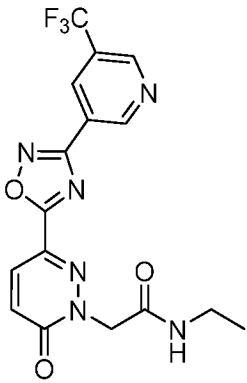
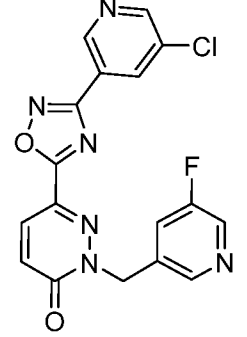
Step 4: 2-[3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-oxo-1,6-dihydropyridazin-1-yl]-N-ethylacetamide

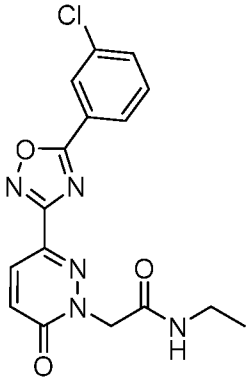
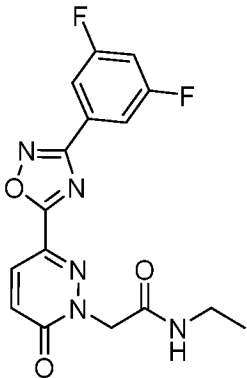
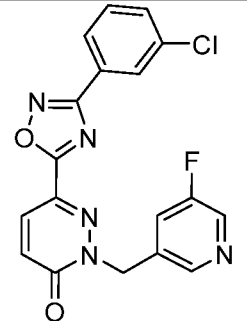
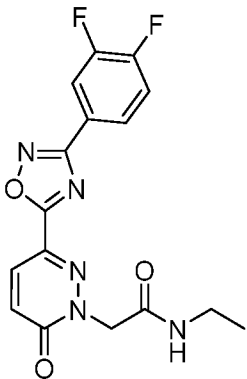
[0267] A solution of methyl 2-[3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-oxo-1,6-dihydropyridazin-1-yl]acetate (120 mg, 0.43 mmol) in ethanamine 35% in EtOH (5 mL) was stirred for 4 h at 80 °C. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to give the title compound as a white solid (64.5 mg, 51.33%). ^1H NMR (300 MHz, Methanol- d_4): δ 8.09 (d, $J = 9.9$ Hz, 1H), 7.16 (d, $J = 9.9$ Hz, 1H), 4.93 (s, 2H), 3.29 (q, $J = 7.2$ Hz, 1H), 2.25-2.15 (m, 1H), 1.29-1.00 (m, 7H). LC/MS: $R_t = 1.782$ min; MS m/z : 290 $[\text{M}+\text{H}]^+$.

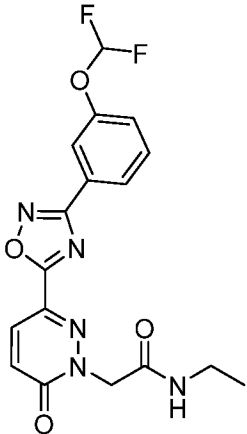
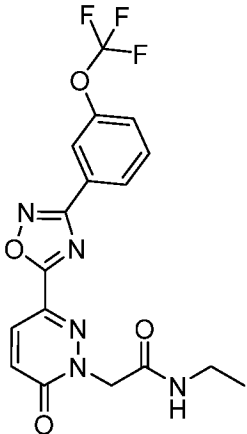
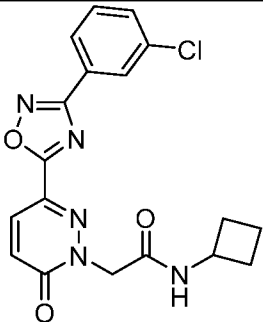
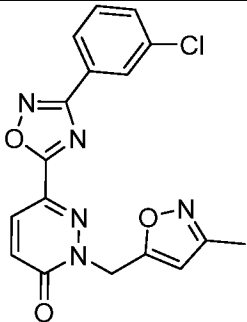
[0268] The following compounds were synthesized following **Example 1**:

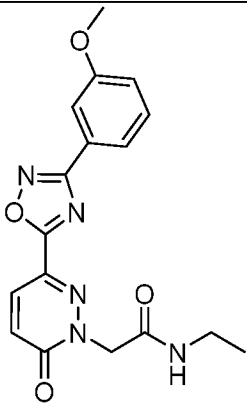
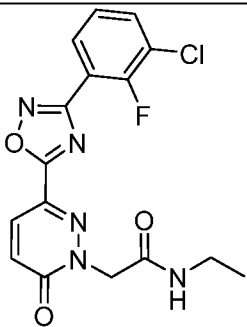
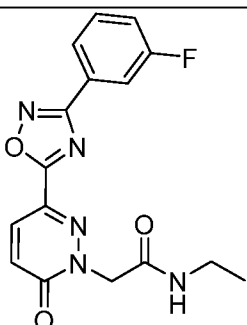
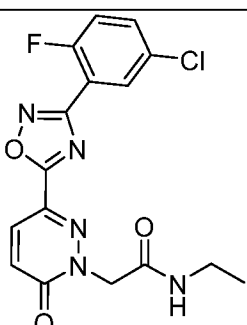
Compound number	Structure	Name	NMR
17		2-[3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	^1H NMR (400 MHz, Methanol- d_4): δ 8.26 (d, $J = 9.6$ Hz, 1H), 8.16 (d, $J = 7.2$ Hz, 2H), 7.58 (m, 3H), 7.22 (d, $J = 9.6$ Hz, 1H), 4.97 (s, 2H), 3.30 (q, $J = 7.2$ Hz, 2H), 1.19 (t, $J = 7.2$ Hz, 3H). LC/MS: $R_t = 3.450$ min; MS m/z : 326 $[\text{M}+\text{H}]^+$.

16		N-ethyl-2-[6-oxo-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,6-dihydropyridazin-1-yl]acetamide	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄): δ 8.26 (d, <i>J</i> = 9.6 Hz, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 2H), 7.58 (m, 3H), 7.22 (d, <i>J</i> = 9.6 Hz, 1H), 4.97 (s, 2H), 3.30 (q, <i>J</i> = 7.2 Hz, 2H), 1.19 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 3.450 min; MS <i>m/z</i> : 326 [M+H] ⁺ .
14		2-[3-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.26 (t, <i>J</i> = 5.4 Hz, 1H), 8.18 (d, <i>J</i> = 9.9 Hz, 1H), 8.07 (m, 2H), 7.74 (dt, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.67 (t, <i>J</i> = 7.8 Hz, 1H), 7.23 (d, <i>J</i> = 9.9 Hz, 1H), 4.84 (s, 2H), 3.20-3.05 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 1.358 min; MS <i>m/z</i> : 360 [M+H] ⁺ .
13		N-ethyl-2-[6-oxo-3-[3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl]pyridazin-1-yl]acetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.26 (d, <i>J</i> = 2.0 Hz, 1H), 8.84 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 8.46 (dt, <i>J</i> = 8.0, 2.0 Hz, 1H), 8.26 (t, <i>J</i> = 5.6 Hz, 1H), 8.18 (d, <i>J</i> = 9.6 Hz, 1H), 7.67 (dd, <i>J</i> = 8.0, 4.8 Hz, 1H), 7.24 (d, <i>J</i> = 9.6 Hz, 1H), 4.85 (s, 2H), 3.20-30.6 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 1.513 min; MS <i>m/z</i> : 327 [M+H] ⁺ .
60		2-benzyl-6-[3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]pyridazin-3-one	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 9.19 (m, 1H), 8.92 (m, 1H), 8.51 (m, 1H), 8.17 (d, <i>J</i> = 9.9 Hz, 1H), 7.49-7.13 (m, 6H), 5.43 (s, 2H). LC/MS: <i>R</i> _t = 1.556 min; MS <i>m/z</i> : 366 [M+H] ⁺ .

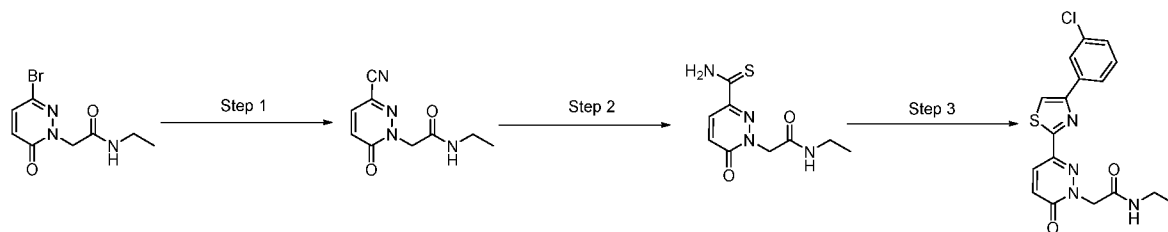
12		2-[3-[3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 9.21 (d, <i>J</i> = 1.8 Hz, 1H), 8.92 (d, <i>J</i> = 2.1 Hz, 1H), 8.53 (t, <i>J</i> = 2.1 Hz, 1H), 8.27 (t, <i>J</i> = 5.7 Hz, 1H), 8.19 (d, <i>J</i> = 9.9 Hz, 1H), 7.24 (d, <i>J</i> = 9.9 Hz, 1H), 4.85 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: R _t = 2.205 min; MS <i>m/z</i> : 361 [M+H] ⁺ .
11		N-ethyl-2-(6-oxo-3-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5-yl)pyridazin-1-ylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.41 (d, <i>J</i> = 7.8 Hz, 1H), 8.34 (m, 1H), 8.26 (t, <i>J</i> = 5.6 Hz, 1H), 8.21 (d, <i>J</i> = 9.9 Hz, 1H), 8.05 (d, <i>J</i> = 8.1 Hz, 1H), 7.89 (t, <i>J</i> = 7.8 Hz, 1H), 7.22 (d, <i>J</i> = 9.9 Hz, 1H), 4.85 (s, 2H), 3.20-3.07 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: R _t = 1.664 min; MS <i>m/z</i> : 394 [M+H] ⁺ .
10		N-ethyl-2-(6-oxo-3-[3-(trifluoromethyl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl)pyridazin-1-ylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 9.55 (d, <i>J</i> = 1.8 Hz, 1H), 9.28 (d, <i>J</i> = 1.8 Hz, 1H), 8.73 (d, <i>J</i> = 2.4 Hz, 1H), 8.33-8.18 (m, 2H), 7.25 (d, <i>J</i> = 9.9 Hz, 1H), 4.85 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: R _t = 2.607 min; MS <i>m/z</i> : 395 [M+H] ⁺ .
65		6-[3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-2-[(5-fluoropyridin-3-yl)methyl]pyridazin-3-one	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 9.20 (d, <i>J</i> = 1.8 Hz, 1H), 8.92 (d, <i>J</i> = 2.4 Hz, 1H), 8.60-8.49 (m, 3H), 8.19 (d, <i>J</i> = 9.9 Hz, 1H), 7.74 (m, 1H), 7.28 (d, <i>J</i> = 9.9 Hz, 1H), 5.52 (s, 2H). LC/MS: R _t = 1.718 min; MS <i>m/z</i> : 385 [M+H] ⁺ .

31		2-[3-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.20 (m, 3H), 8.07 (d, <i>J</i> = 9.9 Hz, 1H), 7.85 (dd, <i>J</i> = 8.4, 1.8 Hz, 1H), 7.72 (t, <i>J</i> = 7.8 Hz, 1H), 7.19 (d, <i>J</i> = 9.6 Hz, 1H), 4.81 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 1.640 min; MS <i>m/z</i> : 360 [M+H] ⁺ .
9		2-[3-[3-(3,5-difluorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.26 (s, 1H), 8.17 (d, <i>J</i> = 9.9 Hz, 1H), 7.81-7.72 (m, 2H), 7.69-7.56 (m, 1H), 7.24 (d, <i>J</i> = 9.6 Hz, 1H), 4.84 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 3.097 min; MS <i>m/z</i> : 362 [M+H] ⁺ .
64		6-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-[(5-fluoropyridin-3-yl)methyl]pyridazin-3-one	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.60-8.48 (m, 2H), 8.19 (d, <i>J</i> = 9.9 Hz, 1H), 8.07 (m, 2H), 7.74 (m, 2H), 7.67 (t, <i>J</i> = 7.8 Hz, 1H), 7.26 (d, <i>J</i> = 9.9 Hz, 1H), 5.52 (s, 2H). LC/MS: <i>R</i> _t = 3.335 min; MS <i>m/z</i> : 384 [M+H] ⁺ .
8		2-[3-[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.25 (t, <i>J</i> = 5.6 Hz, 1H), 8.16 (d, <i>J</i> = 9.6 Hz, 1H), 8.10 (m, 1H), 8.02-7.94 (m, 1H), 7.72 (m, 1H), 7.23 (d, <i>J</i> = 9.6 Hz, 1H), 4.84 (s, 2H), 3.13 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 3.282 min; MS <i>m/z</i> : 362 [M+H] ⁺ .

7		2-(3-[3-(difluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1-yl)-N-ethylacetamide	^1H NMR (400 MHz, DMSO- d_6): δ 8.28 (t, J = 5.6 Hz, 1H), 8.18 (d, J = 10.0 Hz, 1H), 8.02-7.95 (m, 1H), 7.83 (s, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.48 (dd, J = 8.0, 2.4 Hz, 1H), 7.26-7.19 (m, 1H), 4.84 (s, 2H), 3.17-3.10 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 4.741 min; MS m/z : 392 $[\text{M}+\text{H}]^+$.
6		N-ethyl-2-(6-oxo-3-[3-(trifluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl]pyridazin-1-yl)acetamide	^1H NMR (400 MHz, DMSO- d_6): δ 8.28 (t, J = 5.6 Hz, 1H), 8.22-8.11 (m, 2H), 7.99 (s, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.73-7.66 (m, 1H), 7.23 (d, J = 10.0 Hz, 1H), 4.84 (s, 2H), 3.19-3.08 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 2.598min; MS m/z : 410 $[\text{M}+\text{H}]^+$.
5		2-[3-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-cyclobutylacetamide	^1H NMR (300 MHz, DMSO- d_6): δ 8.56 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 9.9 Hz, 1H), 8.11-8.02 (m, 2H), 7.79-7.71 (m, 1H), 7.69-7.64 (m, 1H), 7.22 (d, J = 9.9 Hz, 1H), 4.82 (s, 2H), 4.27-4.14 (m, 1H), 2.23-2.13 (m, 2H), 2.03-1.84 (m, 2H), 1.73-1.55 (m, 2H). LC/MS: R_t = 3.065 min; MS m/z : 386 $[\text{M}+\text{H}]^+$.
63		6-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-[(3-methyl-1,2-oxazol-5-yl)methyl]pyridazin-3-one	^1H NMR (300 MHz, DMSO- d_6): δ 8.19 (d, J = 9.9 Hz, 1H), 8.07 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 9.8 Hz, 1H), 6.42 (s, 1H), 5.56 (s, 2H), 2.22 (s, 3H). LC/MS: R_t = 1.551 min; MS m/z : 370 $[\text{M}+\text{H}]^+$.

4		N-ethyl-2-[3-[3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]acetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.25 (t, <i>J</i> = 5.4 Hz, 1H), 8.17 (d, <i>J</i> = 9.6 Hz, 1H), 7.69 (dd, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.59 (dd, <i>J</i> = 2.8, 1.6 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 (dd, <i>J</i> = 9.6, 2.4 Hz, 2H), 4.84 (s, 2H), 3.87 (s, 3H), 3.18-3.10 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 3.079 min; MS <i>m/z</i> : 356 [M+H] ⁺ .
3		2-[3-[3-(3-chloro-2-fluorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.28 (t, <i>J</i> = 5.4 Hz, 1H), 8.20-8.04 (m, 2H), 7.94-7.88 (m, 1H), 7.50 (t, <i>J</i> = 8.1 Hz, 1H), 7.23 (d, <i>J</i> = 9.7 Hz, 1H), 4.84 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 1.432 min; MS <i>m/z</i> : 378 [M+H] ⁺ .
2		N-ethyl-2-[3-[3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl]-6-oxopyridazin-1-yl]acetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.27 (t, <i>J</i> = 5.4 Hz, 1H), 8.17 (d, <i>J</i> = 9.9 Hz, 1H), 7.94-7.88 (m, 1H), 7.87-7.85 (m, 1H), 7.83-7.68 (m, 1H), 7.58-7.50 (m, 1H), 7.23 (d, <i>J</i> = 9.8 Hz, 1H), 4.84 (s, 2H), 3.21-3.06 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 1.500 min; MS <i>m/z</i> : 344 [M+H] ⁺ .
1		2-(3-(3-(5-chloro-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 12.38 (s, 1H), 8.86 (s, 2H), 8.54-8.52 (m, 2H), 7.99 (d, <i>J</i> = 9.9 Hz, 1H), 7.79-7.74 (m, 1H), 7.09 (d, <i>J</i> = 9.9 Hz, 1H), 5.36 (s, 2H). LC/MS: <i>R</i> _t = 0.872 min; MS <i>m/z</i> : 378 [M+H] ⁺ .

Example 2: 2-(3-(4-(3-chlorophenyl)thiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide (Compound 81)



Step 1: 2-(3-cyano-6-oxopyridazin-1-yl)-N-ethylacetamide

[0269] To a stirred solution of 2-(3-bromo-6-oxopyridazin-1-yl)-N-ethylacetamide (1.00 g, 0.38 mmol) in DMA (10.00 mL) were added $\text{Zn}(\text{CN})_2$ (496.70 mg, 0.42 mmol), XantPhos (222.47 mg, 0.038 mmol) and DIPEA (49.69 mg, 0.038 mmol). The resulting solution was stirred for 16 h at 100°C. The reaction was diluted by the addition of H_2O (30 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow solid (499 mg, 63.07%) MS m/z : 207 $[\text{M}+\text{H}]^+$.

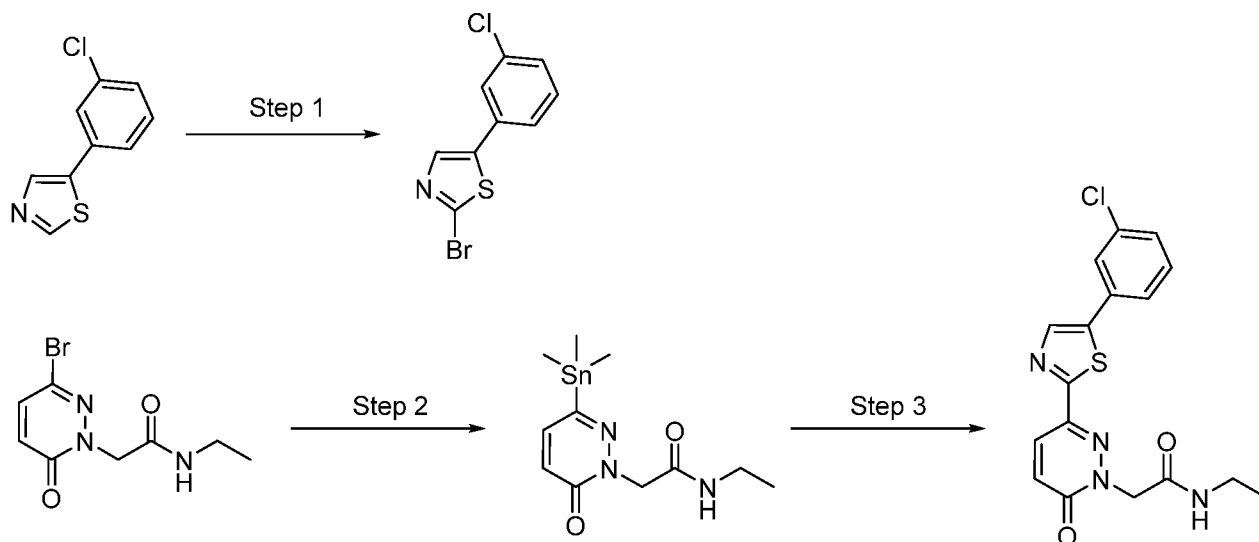
Step 2: 2-(3-carbamothioyl-6-oxopyridazin-1-yl)-N-ethylacetamide

[0270] To a stirred solution of 2-(3-cyano-6-oxopyridazin-1-yl)-N-ethylacetamide (200.00 mg, 0.097 mmol) in EtOH (2.00 mL) was added P_2S_5 (431.17 mg, 0.19 mmol). The resulting solution was stirred for 3 h at 80°C. The reaction was quenched by the addition of H_2O (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a white solid (150 mg, 64.36%) MS m/z : 241 $[\text{M}+\text{H}]^+$.

Step 3: 2-(3-(4-(3-chlorophenyl)thiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide

[0271] To a stirred solution of 2-(3-carbamothioyl-6-oxopyridazin-1-yl)-N-ethylacetamide (100.00 mg, 0.083 mmol) in ethanol (3.00 mL) was added 2-bromo-1-(3-chlorophenyl)ethanone (106.89 mg, 0.092 mmol). The resulting solution was stirred for 2 h at 80°C. The reaction was diluted by the addition of H_2O (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC to give the title compound as a white solid (50 mg, 32.05%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.43 (s, 1H), 8.30 (d, $J = 9.6$ Hz, 1H), 8.22 (t, $J = 5.2$ Hz, 1H), 8.14 (t, $J = 2.0$ Hz, 1H), 8.04 (m, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.46 (m, 1H), 7.16 (d, $J = 9.6$ Hz, 1H), 4.74 (s, 2H), 3.13 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H). LC/MS: $R_t = 2.571$ min; MS m/z : 375 $[\text{M}+\text{H}]^+$.

Example 3: 2-[3-[5-(3-chlorophenyl)-1,3-thiazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide (Compound 25)



Step 1: 2-bromo-5-(3-chlorophenyl)-1,3-thiazole

[0272] To a stirred solution of 5-(3-chlorophenyl)-1,3-thiazole (600.00 mg, 1.02 mmol) in THF (3.00 mL) were added LDA (492.75 mg, 1.53 mmol) and CBr_4 (1525.42 mg, 1.533 mmol) at -78°C . The resulting solution was stirred for 30 min at -78°C and 1 h at room temperature. The reaction was quenched by the addition of sat. aqueous NH_4Cl (aq.) (20 mL) solution at 0°C . The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow solid (800 mg, 95.02%) MS m/z : 274 $[\text{M}+\text{H}]^+$.

Step 2: N-ethyl-2-[6-oxo-3-(trimethylstannyl)pyridazin-1-yl]acetamide

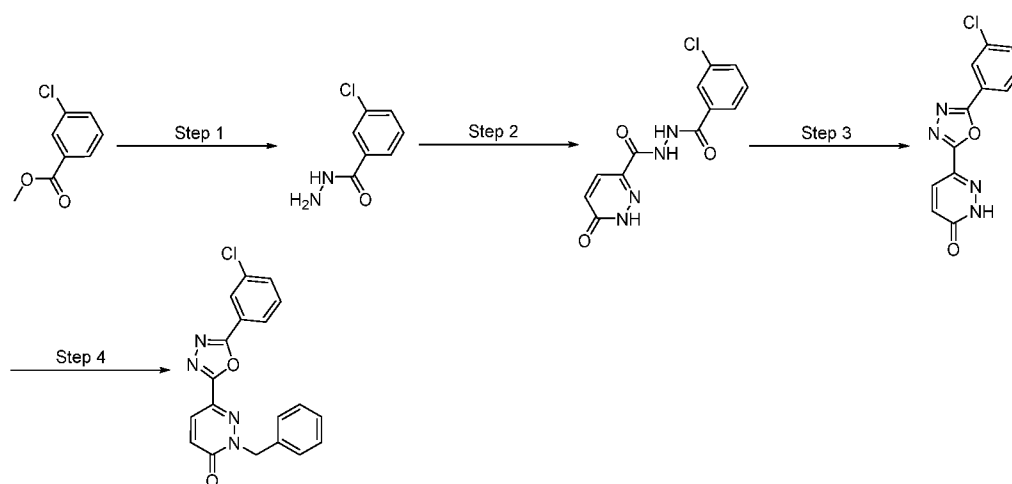
[0273] To a stirred solution of 2-(3-bromo-6-oxopyridazin-1-yl)-N-ethylacetamide (1.00 g, 3.85 mmol) in Dioxane (5.00 mL) were added hexamethyldistannane (2.52 g, 7.69 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (281.32 mg, 0.38 mmol). The reaction was stirred for 1 h at 100°C under Argon atmosphere. The resulting mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography to give the title compound as a yellow solid (800 mg, 60.49%) MS m/z : 346 $[\text{M}+\text{H}]^+$.

Step 3: 2-[3-[5-(3-chlorophenyl)-1,3-thiazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide

[0274] To a stirred solution of N-ethyl-2-[6-oxo-3-(trimethylstannyl)pyridazin-1-yl]acetamide (200.00 mg, 0.58 mmol) in dioxane (2.00 mL) were added $\text{Pd}(\text{dppf})\text{Cl}_2$ (212.70 mg, 0.29 mmol) and 2-bromo-5-(3-chlorophenyl)-1,3-thiazole (319.25 mg, 1.16 mmol). The reaction was stirred for 3 h at 100°C under Argon atmosphere. The reaction was quenched by the addition of H_2O (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The

combined organic layers were washed by water (20 mL), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The crude product was first purified by silica gel column chromatography and then further purified by Prep-HPLC to give the title compound as a off-white solid (17.1 mg, 7.85%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.51 (s, 1H), 8.20 (t, J = 5.6 Hz, 1H), 8.14 (d, J = 9.6 Hz, 1H), 7.92 (t, J = 2.0 Hz, 1H), 7.72 (dd, J = 7.2, 1.6 Hz, 1H), 7.55-7.44 (m, 2H), 7.15 (d, J = 9.7 Hz, 1H), 4.73 (s, 2H), 3.20-3.08 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 2.576 min; MS m/z : 375 $[\text{M}+\text{H}]^+$.

Example 4: 2-benzyl-6-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)pyridazin-3(2H)-one (Compound 73)



Step 1: 3-chlorobenzohydrazide

[0275] To a stirred solution of methyl 3-chlorobenzoate (3.00 g, 17.58 mmol) in MeOH (10.00 mL) was added Hydrazine Monohydrate (3.0 mL). The reaction mixture was stirred for 2 h at 50°C . The precipitated solids were collected by filtration and washed with ACN (3x3 mL) to give the title compound as a off-white solid (2.5 g, 83.33%) MS m/z : 171 $[\text{M}+\text{H}]^+$.

Step 2: N-(3-chlorobenzoyl)-6-oxo-1H-pyridazine-3-carbohydrazide

[0276] To a stirred solution of 3-chlorobenzohydrazide (500.00 mg, 2.93 mmol) in DMF (5.00 mL) were added 6-oxo-1H-pyridazine-3-carboxylic acid (451.66 mg, 3.22 mmol), HATU (1.33 g, 3.52 mmol) and DIEA (1.14 g, 8.79 mmol). The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (10 mL). The precipitated solids were collected by filtration and washed with ACN (3x3 mL) to give the title compound as a white solid (400 mg, 46.63%) MS m/z : 293 $[\text{M}+\text{H}]^+$.

Step 3: 6-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2H-pyridazin-3-one

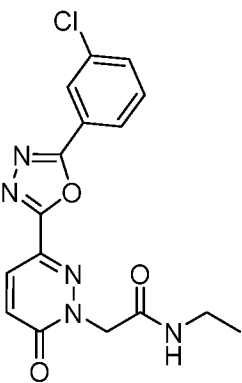
[0277] To a stirred solution of N-(3-chlorobenzoyl)-6-oxo-1H-pyridazine-3-carbohydrazide (330 mg, 1.13 mmol) in toluene (3.00 mL) was added POCl_3 (0.32 mL, 3.43 mmol). The reaction

mixture was stirred overnight at 100°C. The reaction was quenched by the addition of water (15 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a brown solid (280 mg, 90.42%) MS *m/z*: 275 [M+H]⁺.

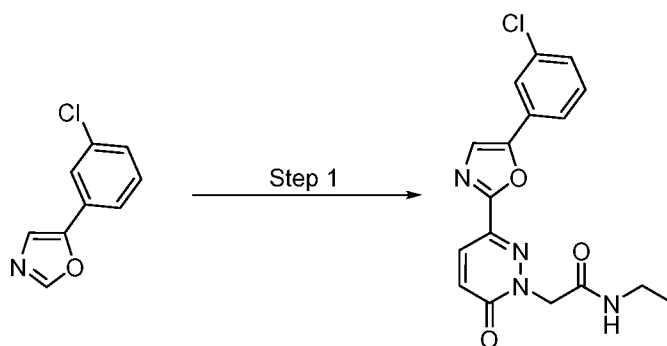
Step 4: 2-benzyl-6-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]pyridazin-3-one

[0278] To a stirred solution of 6-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2H-pyridazin-3-one (120.00 mg, 0.44 mmol) in DMF (2.0 mL) were added benzyl bromide (82.20 mg, 0.48 mmol) and K₂CO₃ (181.15 mg, 1.31 mmol). The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (10 mL). The precipitated solids were collected by filtration. The crude product was purified by Prep-HPLC to give the title compound as a white solid (30 mg, 18.82%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.18 (d, *J* = 9.6 Hz, 1H), 8.12-8.03 (m, 2H), 7.79-7.76 (m, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 4H), 7.79-7.71 (m, 1H), 7.24 (d, *J* = 9.6 Hz, 1H), 5.42 (s, 2H). LC/MS: R_t = 2.443 min; MS *m/z*: 365 [M+H]⁺.

[0279] The following compound was synthesized following **Example 4**:

Compound number	Structure	Name	NMR
29		2-[3-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.24 (t, <i>J</i> = 5.4 Hz, 1H), 8.17 (d, <i>J</i> = 9.9 Hz, 1H), 8.06 (dd, <i>J</i> = 7.5, 1.5 Hz, 2H), 7.76 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.68 (t, <i>J</i> = 7.8 Hz, 1H), 7.21 (d, <i>J</i> = 9.9 Hz, 1H), 4.82 (s, 2H), 3.14-3.10 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: R _t = 1.411 min; MS <i>m/z</i> : 360 [M+H] ⁺ .

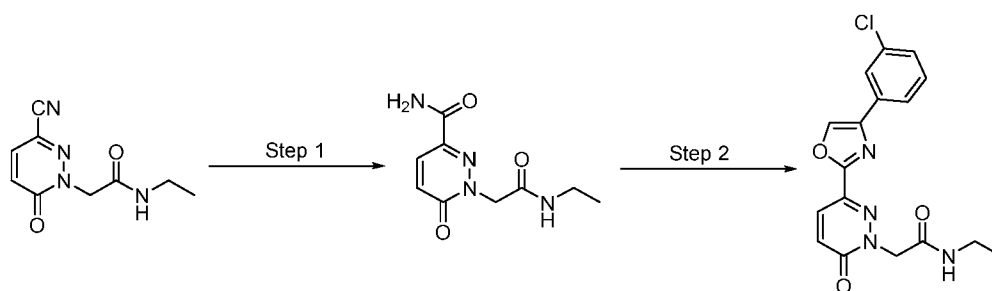
Example 5: 2-[3-[5-(3-chlorophenyl)-1,3-oxazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide (Compound 27)



Step 1: 2-[3-[5-(3-chlorophenyl)-1,3-oxazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide

[0280] To a stirred solution of 5-(3-chlorophenyl)-1,3-oxazole (200.00 mg, 1.11 mmol) in DMA (2.00 mL) were added 2-(3-bromo-6-oxopyridazin-1-yl)-N-ethylacetamide (318.6 mg, 1.23 mmol), K_2CO_3 (384.76 mg, 2.78 mmol), PPh_3 (58.42 mg, 0.22 mmol), CuI (127.25 mg, 0.67 mmol) and $Pd(OAc)_2$ (25.00 mg, 0.011 mmol). The resulting reaction mixture was irradiated under microwave radiation conditions for 1 h at 120°C. The reaction was diluted by the addition of H_2O (20 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography and then further purified by Prep-HPLC to give the title compound as a white solid (35 mg, 8.76%). ^1H NMR (400 MHz, $DMSO-d_6$): δ 8.21 (t, $J = 5.4$ Hz, 1H), 8.12 (d, $J = 9.6$ Hz, 1H), 8.07 (s, 1H), 7.91 (t, $J = 2.0$ Hz, 1H), 7.79 (d, $J = 7.6$, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.46-7.43 (m, 1H), 7.15 (d, $J = 10.0$ Hz, 1H), 4.79 (s, 2H), 3.15-3.10 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H). LC/MS: $R_t = 1.389$ min; MS m/z : 359 $[M+H]^+$.

Example 6: 2-[3-[4-(3-chlorophenyl)-1,3-oxazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide (Compound 30)



Step 1: 1-[(ethylcarbamoyl)methyl]-6-oxopyridazine-3-carboxamide

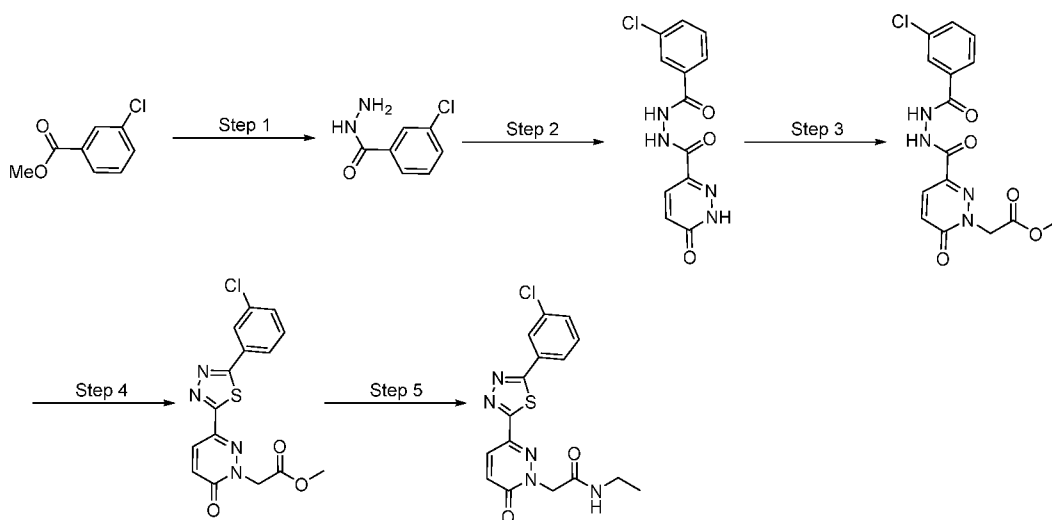
[0281] A solution of 2-(3-cyano-6-oxopyridazin-1-yl)-N-ethylacetamide (200.00 mg, 0.10 mmol) in sulfuric acid (2.0 mL) was stirred for 1 h at 50°C. The pH value of the solution was adjusted to 7 with NaOH (1 mol/L). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product

was purified by silica gel column chromatography to give the title compound as a white solid (150 mg, 68.97%) MS m/z : 225 $[M+H]^+$.

Step 2: 2-[3-[4-(3-chlorophenyl)-1,3-oxazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide

[0282] To a stirred solution of was 1-[(ethylcarbamoyl)methyl]-6-oxopyridazine-3-carboxamide (100.00 mg, 0.22 mmol) in Toluene (5.00 mL) was added 2-bromo-1-(3-chlorophenyl)ethanone (114.55 mg, 0.25 mmol). The reaction mixture was stirred for 2 days at 120 degrees C. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by Prep-HPLC to give the title compound as a white solid (11.7 mg, 7.31%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.87 (s, 1H), 8.21 (t, J = 5.6 Hz, 1H), 8.13 (d, J = 9.6 Hz, 1H), 7.92 (t, J = 2.0 Hz, 1H), 7.83 (d, J = 7.6, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.46-7.43 (m, 1H), 7.15 (d, J = 10.0 Hz, 1H), 4.77 (s, 2H), 3.15-3.10 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 1.399 min; MS m/z : 359 $[M+H]^+$.

Example 7: 2-[3-[5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide (Compound 24)



Step 1: benzoylhydrazine, M-chloro

[0283] To a stirred solution of methyl 3-chlorobenzoate (600.00 mg, 3.53 mmol) in methanol (5.00 mL) was added Hydrazine Monohydrate (1.0 mL). The resulting solution was stirred for 1 h at 70°C. The precipitated solids were collected by filtration and washed with ACN (2x2 mL) to give the title compound as a off-white solid (550 mg, 91.67%) MS m/z : 171 $[M+H]^+$.

Step 2: 3-chloro-N-(6-oxo-1H-pyridazine-3-carbonyl)benzohydrazide

[0284] To a stirred solution of 6-oxo-1H-pyridazine-3-carboxylic acid (451.66 mg, 3.22 mmol) in DMF (8.00 mL) were added HATU (1.23 g, 3.22 mmol), DIEA (568.19 mg, 4.396 mmol, 1.5 equiv) and benzoylhydrazine, M-chloro (500.00 mg, 2.93 mmol). The resulting solution was

stirred at room temperature for 1 h. The resulting mixture was diluted with water (10 mL). The precipitated solids were collected by filtration and washed with ACN (2x2 mL) to give the title compound as a white solid (350 mg, 40.91%) MS *m/z*: 293 [M+H]⁺.

Step 3: methyl 2-(3-[[3-(3-chlorophenyl)formohydrazido]carbonyl]-6-oxopyridazin-1-yl)acetate

[0285] To a stirred solution of 3-chloro-N-(6-oxo-1H-pyridazine-3-carbonyl)benzohydrazide (175.00 mg, 0.601 mmol) in DMF (2.00 mL) were added K₂CO₃ (167.43 mg, 1.20 mmol) and methyl 2-bromoacetate (82.79 mg, 0.54 mmol). The resulting solution was stirred for 1 h at room temperature. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a white solid (150 mg, 64.97%) MS *m/z*: 365 [M+H]⁺.

Step 4: methyl 2-[3-[5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-6-oxopyridazin-1-yl]acetate

[0286] To a stirred solution of methyl 2-(3-[[3-(3-chlorophenyl)formohydrazido]carbonyl]-6-oxopyridazin-1-yl)acetate (130.00 mg, 0.36 mmol) in Toluene (2.00 mL) were added bis(4-methoxyphenyl)-1,3,2lambda5,4lambda5-dithiadiphosphetane-2,4-dithione (288.31 mg, 0.71 mmol) and TEA (108.20 mg, 1.069 mmol). The resulting solution was stirred for 2h at 100 degrees C. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a white solid (50 mg, 36.73%) MS *m/z*: 363 [M+H]⁺.

Step 5: 2-[3-[5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-6-oxopyridazin-1-yl]-N-ethylacetamide

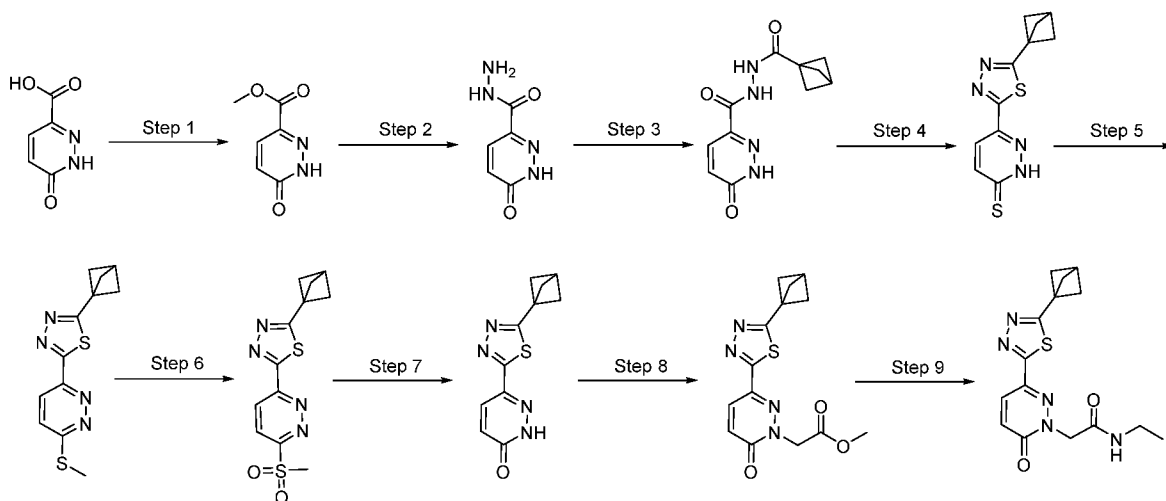
[0287] To a stirred solution of methyl 2-[3-[5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-6-oxopyridazin-1-yl]acetate (47.42 mg, 0.131 mmol) in methanol (1.00 mL) was added ethylamine in EtOH (35%) (1 mL, 0.66 mmol). The resulting solution was stirred for 1 h at 70°C. The residue was filtered to afford 35 mg white solid. The crude product was re-crystallized from MeOH (1.00 mL) to give the title compound as a white solid (25 mg, 48.47%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.26-8.21 (m, 2H), 8.13 (t, *J* = 2.0 Hz, 1H), 8.06-8.04 (m, 1H), 7.72-7.69 (m, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 10 Hz, 1H), 4.76 (s, 2H), 3.14 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H). LC/MS *R*_t = 1.16 min; MS *m/z*: 376 [M+H]⁺.

[0288] The following compound was synthesized following **Example 7**:

Compound number	Structure	Name	IC50 (μM)
23		2-(3-(5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-cyclobutylacetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.51(d, <i>J</i> = 7.8 Hz, 1H), 8.24 (d, <i>J</i> = 10 Hz, 1H), 8.13 (t, <i>J</i> = 1.6 Hz, 1H), 8.04 (d, <i>J</i> = 8.0 Hz, 1H), 7.71-7.69 (m, 1H), 7.63 (t, <i>J</i> = 7.6 Hz, 1H), 7.21 (d, <i>J</i> = 9.6 Hz, 1H), 4.74 (s, 2H), 4.22 - 4.20 (m, 1H), 2.21-2.14 (m, 2H), 1.96-1.90 (m, 2H), 1.68-1.61 (m, 2H). LC/MS: <i>R</i> _t = 1.279 min; MS <i>m/z</i> : 402 [M+H] ⁺ .
22		N-cyclobutyl-2-(6-oxo-3-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)pyridazin-1(6H)-yl)acetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 8.75 (d, <i>J</i> = 4.5 Hz, 1H), 8.52 (d, <i>J</i> = 7.8 Hz, 1H), 8.34 (d, <i>J</i> = 7.8 Hz, 1H), 8.25 (d, <i>J</i> = 9.6 Hz, 1H), 8.11-8.06 (m, 1H), 7.66-7.62 (m, 1H), 7.20 (d, <i>J</i> = 9.9 Hz, 1H), 4.75 (s, 2H), 4.25-4.17 (m, 1H), 2.19-2.17 (m, 2H), 2.00-1.87 (m, 2H), 1.66-1.58 (m, 2H). LC/MS: <i>R</i> _t = 1.663 min; MS <i>m/z</i> : 369 [M+H] ⁺ .
21		2-(3-(5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): δ 9.21 (d, <i>J</i> = 1.8 Hz, 1H), 8.87 (d, <i>J</i> = 2.4 Hz, 1H), 8.61 (t, <i>J</i> = 2.1 Hz, 1H), 8.27-8.21 (m, 2H), 7.20(d, <i>J</i> = 9.6 Hz, 1H), 4.77 (s, 2H), 3.18-3.09 (m, 2H), 1.06 (t, <i>J</i> = 7.2 Hz, 3H). LC/MS: <i>R</i> _t = 2.672 min; MS <i>m/z</i> : 377 [M+H] ⁺ .
20		2-(3-(5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-cyclobutylacetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.20 (d, <i>J</i> = 2.0 Hz, 1H), 8.86 (d, <i>J</i> = 2.4 Hz, 1H), 8.60 (t, <i>J</i> = 2.0 Hz, 1H), 8.50 (d, <i>J</i> = 7.6 Hz, 1H), 8.25 (d, <i>J</i> = 9.6 Hz, 1H), 7.21 (d, <i>J</i> = 10 Hz, 1H), 4.75 (s, 2H), 4.21 (h, <i>J</i> = 8.0 Hz, 1H), 2.19-2.17 (m, 2H), 1.96-1.90 (m, 2H), 1.66-1.64 (m, 2H). LC/MS: <i>R</i> _t = 1.438 min; MS <i>m/z</i> : 403 [M+H] ⁺ .

19		N-ethyl-2-(6-oxo-3-(5-(5-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)pyridazin-1(6H)-yl)acetamide	^1H NMR (400 MHz, DMSO- d_6): δ 9.54 (d, J = 2.0 Hz, 1H), 9.21 (d, J = 0.8 Hz, 1H), 8.81 (s, 1H), 8.28-8.23 (m, 2H), 7.23 (d, J = 9.6 Hz, 1H), 4.77 (s, 2H), 3.15-3.12 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 1.384 min; MS m/z : 411 $[\text{M}+\text{H}]^+$.
18		N-cyclobutyl-2-(3-(5-(2,5-dichlorophenyl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide	^1H NMR (400 MHz, DMSO- d_6): δ 8.51 (d, J = 7.6 Hz, 1H), 8.30-8.26 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 8.8, 2.4 Hz, 1H), 7.22 (d, J = 10 Hz, 1H), 4.76 (s, 2H), 4.20 (q, J = 8.0 Hz, 1H), 2.21-2.14 (m, 2H), 1.98-1.88 (m, 2H), 1.68-1.61 (m, 2H). LC/MS: R_t = 3.223 min; MS m/z : 436 $[\text{M}+\text{H}]^+$.

Example 8: 2-[3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1-yl]-N-ethylacetamide (Compound 32)



Step 1: methyl 6-oxo-1H-pyridazine-3-carboxylate

[0289] To a stirred solution of 6-methoxypyridazine-3-carboxylic acid (1.50 g, 9.732 mmol) in MeOH (50.00 mL) was added H_2SO_4 (1.00 mL). The reaction mixture was stirred for overnight at 50°C . The reaction mixture was allowed to cool down to room temperature. The reaction was diluted by the addition of H_2O (200 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous

Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a white solid (1.20 g, 73.33%) MS *m/z*: 155 [M+H]⁺.

Step 2: 6-oxo-1H-pyridazine-3-carbohydrazide

[0290] To a stirred solution of methyl 6-oxo-1H-pyridazine-3-carboxylate (800.00 mg, 5.19 mmol) in EtOH (5.00 mL) was added Hydrazine Monohydrate (1.0 mL). The reaction mixture was stirred for 3 h at 40°C. The reaction mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with ACN (2x2 mL) to give the title compound as a white solid (650 mg, 81.25%) MS *m/z*: 155 [M+H]⁺.

Step 3: N'-[bicyclo[1.1.1]pentane-1-carbonyl]-6-oxo-1H-pyridazine-3-carbohydrazide

[0291] To a stirred solution of 6-oxo-1H-pyridazine-3-carbohydrazide (500.00 mg, 3.24 mmol) in DMF (8.00 mL) were added bicyclo[1.1.1]pentane-1-carboxylic acid (363.30 mg, 3.24 mmol), PyBOP (2.19 g, 4.21 mmol) and DIPEA (1.26 g, 9.72 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction was diluted by the addition of H₂O (12.0 mL). The precipitated solids were collected by filtration and washed with ACN (2x2 mL) to give the title compound as a white solid (450 mg, 48.90%) MS *m/z*: 249 [M+H]⁺.

Step 4: 6-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-2H-pyridazine-3-thione

[0292] To a stirred solution of N-[bicyclo[1.1.1]pentane-1-carbonyl]-6-oxo-1H-pyridazine-3-carbohydrazide (400.00 mg, 1.61 mmol) in Toluene (5.00 mL) was added Lawesson Reagent (977.60 mg, 2.42 mmol). The reaction mixture was stirred for 1 h at 60 °C. The reaction mixture was allowed to cool down to room temperature. The reaction was diluted by the addition of H₂O (30 mL). The resulting mixture was extracted with EtOAc (3 x20 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow solid (300 mg, 75.59%) MS *m/z*: 263 [M+H]⁺.

Step 5: 3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-(methylsulfanyl)pyridazine

[0293] To a stirred solution of 6-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-2H-pyridazine-3-thione (300.00 mg, 1.14 mmol) in DMF (5.00 mL) were added CH₃I (194.77 mg, 1.37 mmol) and K₂CO₃ (316.08 mg, 2.29 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow solid (260 mg, 82.27%) MS *m/z*: 277 [M+H]⁺.

Step 6: 3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-methanesulfonylpyridazine

[0294] To a stirred solution of 3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-(methylsulfonyl)pyridazine (280.00 mg, 1.01 mmol) in DCM (6.00 mL) was added M-CPBA (524.48 mg, 3.04 mmol). The reaction mixture was stirred for 2 h at 40°C. The reaction mixture was allowed to cool down to room temperature. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with DCM (3x10 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow light solid (260 mg, 83.22%) MS *m/z*: 309 [M+H]⁺.

Step 7: 6-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-2H-pyridazin-3-one

[0295] To a stirred solution of 3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-methanesulfonylpyridazine (220.00 mg, 0.71 mmol) in THF (2.00 mL) were added H₂O (1.00 mL) and KOH (160.11 mg, 2.85 mmol). The reaction mixture was stirred for 2 h at 70°C. The reaction mixture was allowed to cool down to room temperature. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a yellow light solid (160 mg, 91.06%) MS *m/z*: 247 [M+H]⁺.

Step 8: methyl 2-[3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1-yl]acetate

[0296] To a stirred solution of 6-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-2H-pyridazin-3-one (150.00 mg, 0.61 mmol) in DMF (5.00 mL) were added methyl 2-bromoacetate (102.48 mg, 0.67 mmol) and K₂CO₃ (168.34 mg, 1.22 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction was diluted by the addition of H₂O (20 mL). The aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were combined concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the title compound as a white solid (160 mg, 82.22%) MS *m/z*: 319 [M+H]⁺.

Step 9: 2-[3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1-yl]-N-ethylacetamide

[0297] To a stirred solution of methyl 2-[3-(5-[bicyclo[1.1.1]pentan-1-yl]-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1-yl]acetate (160 mg, 0.50 mmol) in EtOH (4 mL) were added DMAP (6.14 mg, 0.05 mmol) and ethylamine in EtOH (35%) (1 mL). The reaction mixture was stirred for overnight at 70°C. The reaction mixture was allowed to cool down to room temperature. The

precipitated solids were collected by filtration and washed with ACN (2x2 mL) to give the title compound as a white solid (95.6 mg, 56.65%). ^1H NMR (300 MHz, DMSO- d_6): δ 8.22-8.15 (m, 2H), 7.16 (d, J = 9.6 Hz, 1H), 4.71 (s, 2H), 3.16-3.07 (m, 2H), 2.64 (s, 1H), 2.29 (s, 6H), 1.04 (t, J = 7.2 Hz, 3H). LC/MS: R_t = 1.325 min; MS m/z : 332 $[\text{M}+\text{H}]^+$.

Example 9. Skeletal Myofibril ATPase Assay

[0298] Overview: Myosin ATPase activity was assessed by using a coupled reaction system, in which ADP generated by the myosin ATPase function was coupled to the disappearance of NADH through the pyruvate kinase/lactate dehydrogenase (PK-LDH) system. Myosin ATPase activity produces ADP, which was used as a substrate for PK to produce pyruvate and regenerate ATP. The pyruvate was then used as a substrate by LDH to oxidize NADH to NAD^+ . The rate of the reaction was monitored through the time-dependent disappearance of NADH using absorbance at 340 nm. Inhibition of ATPase activity by the assayed compounds was indicated by a reduced rate of NADH loss, relative to vehicle-treated controls, over the experimental time window. To assess the selectivity of the assayed compounds for skeletal myofibrils, the compounds were counter-screened in cardiac myofibrils.

[0299] Materials: The following stock solutions and reagents were used in the Skeletal Myofibril ATPase Assay:

<i>Stock Solutions</i>
PIPES, 200 mM in H_2O , pH 7.0
MgCl_2 in H_2O , 200 mM
PM12 Buffer, 10X : 12 mM PIPES (from 200 mM stock), 20 mM MgCl_2 (from 200 mM stock)
EGTA in H_2O , 500 mM
CaCl_2 in H_2O , 500 mM
DTT in H_2O , 1 M
BSA in H_2O , 20 mg/mL
KCl in H_2O , 600 mM
ATP in 1X PM12, 100 mM
NADH in 1X PM12, 30 mM
PEP in 1X PM12, 100 mM, pH 7.0
Antifoam 204, 1% in H_2O

[0300] Stock Solutions of pCa buffer. Combine PIPES, CaCl_2 , and EGTA solutions with 70 mL of water. Adjust pH to 7.0 and bring final volume to 100 mL.

PREPARATION OF STOCKS SOLUTIONS FOR 100 ML OF PCA BUFFER				
pCA	200 mM PIPES (mL)	Approx. Water (mL)	CaCl ₂	EGTA
4.0	6	74	10.025	9.975
4.5	6	74	9.800	10.200
5.0	6	74	9.325	10.675
5.5	6	74	8.100	11.900
5.75	6	74	7.200	12.800
6.0	6	74	6.000	14.000
6.25	6	74	4.500	15.500
6.5	6	74	3.025	16.975
6.75	6	74	1.975	18.025
7.0	6	74	1.165	18.835
8.0	6	74	0.126	19.874
10.0	6	74	0.001	19.999

[0301] Buffer A & Buffer B. Buffers were stored on ice until use.

[0302] Buffer Preparation

Total Well Volume (μ L)	Component	Stock Concentrations Value Unit	Final Concentrations in Specific Buffer	Reaction Concentrations
Buffer A (μ L)	50			
	PM12 Buffer	10 x	1.00 x	1.00 x
	KCl	600 mM	60.00 mM	60.00 mM
	BSA	20 mg/mL	0.10 mg/mL	0.10 mg/mL
	DTT	1000 mM	1.00 mM	1.00 mM
	PK/LDH	80 mM	0.80 mM	0.40 mM
	Rabbit Psoas Prep 11	5.83 mg/mL	0.50 mg/mL	0.25 mg/mL
	Antifoam	1.00 %	0.01 %	0.01 %
Buffer B (μ L)	25			
	PM12 Buffer	10 x	1.00 x	1.00 x
	pCa Solution	10 x	2.00 x	1.00 x
	KCl	600 mM	60.00 mM	60.00 mM
	BSA	20 mg/mL	0.10 mg/mL	0.10 mg/mL
	DTT	1000 mM	1.00 mM	1.00 mM
	ATP	100 mM	0.10 mM	0.05 mM
	NADH	30 mM	1.00 mM	0.50 mM
	PEP	100 mM	3.00 mM	1.50 mM
	Antifoam	1.00 %	0.01 %	0.01 %
	Water			

Total Well Volume (μL)		Number of Wells			
		Volume per well (μL)	Total Volume (μL)	Prepare Volume (μL)	
Buffer A (μL)	25	PM12 Buffer	2.50	240.00	312.00 PM12 Buffer (1 x)
		KCl	2.50	240.00	312.00 KCl (60 mM)
		BSA	0.13	12.00	15.60 BSA (0.1 mg/mL)
		DTT	0.03	2.40	3.12 DTT (1 mM)
		PK/LDH	0.25	24.00	31.20 PK/LDH (0.4 mM)
		Rabbit Psoas Prep 11	2.14	205.83	267.58 Rabbit Psoas Prep 11 (0.25 mg/mL)
		Antifoam	0.25	24.00	31.20 Antifoam (0.01 %)
		Water	17.21	1651.77	2147.30 Water
		25.00	2400.00	3120.00	
Buffer B (μL)	25	PM12 Buffer	2.50	240.00	312.00 PM12 Buffer (1 x)
		pCa Solution	5.00	480.00	624.00 pCa Solution (1 x)
		KCl	2.50	240.00	312.00 KCl (60 mM)
		BSA	0.13	12.00	15.60 BSA (0.1 mg/mL)
		DTT	0.03	2.40	3.12 DTT (1 mM)
		ATP	0.03	2.40	3.12 ATP (0.05 mM)
		NADH	0.83	80.00	104.00 NADH (0.5 mM)
		PEP	0.75	72.00	93.60 PEP (1.5 mM)
		Antifoam	0.25	24.00	31.20 Antifoam (0.01 %)
		Water	12.99	1247.20	1621.36 Water ()
		25.00	2400.00	3120.00	Total

[0303] Skeletal Myofibril ATPase Assay Procedure: BSA, ATP, NADH, PEP, and DTT solutions were thawed at room temperature, then transferred to ice. Pellet-frozen myofibrils (approximately twice the required volume) were transferred into a sufficiently large tube and capped. Myofibrils were thawed by rolling in a water bath for approximately 15 min at room temperature and cooled on ice. Buffers A and B were prepared by adjusting volumes as necessary for required number of wells and stored on ice. 0.5 μL of the compounds to be assayed were added into wells of a 384-well plate. Buffers A and B were mixed by inversion immediately prior to use, then 25 μL of each was dispensed using a Multidrop dispenser (Buffer A first, then Buffer B). The absorbance within the wells was measured at 340 nm, using a kinetic protocol in which the wells are read every 1.5 – 2 min for 1 h. The reaction rate was qualitatively assessed by subtracting the minimum absorbance value from the maximum value for each well, using either the SoftMax Pro plate reader software or a spreadsheet program such as Excel. Using GraphPad Prism 8.0, the data was normalized, with 100% activity defined as the absorbance change in the 1% DMSO vehicle wells and 0% assigned to no change in absorbance over the course of the experiment. The normalized data were fit to a variable-slope four-parameter logistic model, constraining the bottom to be 0 or greater. Compounds of Table 1 to 3 were tested and results of the assay appear in Table 4 herein. A = IC₅₀ is less than or equal to 10 μM; B = IC₅₀ is greater than 10 μM and less than 100 μM; C = IC₅₀ is greater than 100 μM.

Example 10: Comparison of Biomarkers in Muscular Dystrophies

[0304] Healthy volunteer (HV) frozen plasma samples were purchased from BioIVT (Westbury, NY). Plasma and serum for affected individuals were received from the Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases (Duchenne muscular dystrophy), and a Becker muscular dystrophy biomarker study at Binghamton University – SUNY (Becker muscular dystrophy). Upon receipt, all samples were aliquoted into working volumes of 50 – 100 μ L and stored at -80°C to minimize freeze-thaw damage. Red top serum vacutainer tubes, containing silica act clot activator, were used for the blood collection. If a subject required MLPA testing, an EDTA tube would be added for those collections, but was not used for any other analysis. After the serum tubes were left to clot for 30 minutes, they were processed in a centrifuge at 1000-1300xg for 10 minutes. The serum (top layer) fluid was then pipetted from the vacutainer tube and transferred into cryovials and immediately frozen on dry ice for shipment and later storage at -80°C. Serum samples were sent frozen on dry ice to Binghamton University and stored at -80°C. Samples were collected from 2017 to 2019 and analyzed in 2019. Plasma samples from the Newcastle MRC Centre Biobank were collected from patients attending clinics at The John Walton Muscular Dystrophy Research Centre. Blood was drawn into vacutainers, gently inverted 5-10 times to ensure adequate mixing of blood with EDTA and then centrifuged at 1,500xg for 10 minutes. The upper plasma fraction was transferred via pipette into cryovials and immediately stored at -80°C. Samples were collected over a period of 9 years (2010 – 2019) and stored at -80°C prior to analysis.

Creatine Kinase Assay

[0305] Blood plasma CK activity was assayed using a coupled-reaction kit purchased from Pointe Scientific (Canton, MI). Plasma was diluted 25-fold with phosphate-buffered saline (PBS), of which 2 μ L was added to the 384-well plate. The CK assay reagent (70 μ L, 4:1 kit Buffer A:Buffer B) was added using the Multidrop Combi (ThermoFisher, Inc., Waltham, MA) and the reaction progress monitored by absorbance at 340 nm for 30 min with the SpectraMax M3 plate reader (Molecular Devices, San Jose, CA) over approximately 20 – 30 min. Following the termination of the reaction, pathlength correction values were measured with near-IR absorbance at 900 nm and 975 nm. The raw absorbance data were processed in Microsoft Excel to exclude points with $A_{340} > 2.5$ and to correct for pathlength using a system-specific K-Factor of 0.168. The corrected absorbance data versus time was fit to a linear model in GraphPad Prism (GraphPad Software, San Diego, CA) to yield reaction slopes, which were compared to a

standard curve of NADH (5–100 μM) to yield enzyme rates in U/L, where U is defined as the amount of enzyme that results in the reduction of 1 $\mu\text{mol} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$ NADP.

TNNI ELISAs

[0306] Plasma concentrations of TNNI isoforms for slow and fast muscle were measured by capture ELISA. The slow isoform (TNNI1) was measured using a commercially available test kit (LSF7068, LifeSpan Biosciences, Inc, Seattle, WA) and was performed according to the manufacturer's instructions. The fast isoform (TNNI2) was assayed as described previously. Briefly, high-binding ELISA plates were coated with α -TNNI2 monoclonal antibody (Clone 7G2, OriGene, Inc., Rockville, MD) at a concentration 6.4 $\mu\text{g/mL}$ overnight at 4°C. The wells were blocked with 1% w/v non-fat dry milk in PBS for 30 min at 37°C., followed by incubation for 2 h at 37°C with the samples or recombinant human TNNI2 as a standard curve. The wells were washed with PBS containing 0.1% Tween-20 (PBS-T) and incubated with 1 $\mu\text{g/mL}$ polyclonal α -TNNI2 antibody (PA5-76303, ThermoFisher, Inc.) for 90 min at 37°C. After washing with PBS-T, the detection antibody (HRP-conjugated goat- α -rabbit IgG, 0.08 $\mu\text{g/mL}$, Pierce Biosciences) was added for 45 min at 37°C and the HRP was visualized with Ultra-TMB colorimetric reagent (ThermoFisher) followed by quenching with 2 N H_2SO_4 and measurement of the absorbance at 410 nm. Selectivity of these assays for fast versus slow TNNI has previously been confirmed using human muscle extracts.

[0307] These studies show the relation of skeletal muscle biomarkers in DMD and BMD patient plasma.

[0308] Figure 3. Plasma concentrations of creatine kinase (CK) enzymatic activity (A), fast skeletal troponin I (TNNI1) (B), and slow skeletal TNNI2 (C) were measured in samples from Becker muscular dystrophy (BMD, squares) and Duchenne muscular dystrophy (DMD) patients (triangles), with healthy volunteers as controls (circles). In each panel, the error bars represent the median $\pm$ the interquartile range. In panels B and C, samples that exhibited no detectable TNNI concentration were assigned values equal to the assay's limit of detection (0.1 ng/mL and 0.001 ng/mL for fast and slow TNNI, respectively) When compared with each other, a significant correlation was found between CK and fast TNNI2 (D), with an R^2 of 0.67. There was no significant correlation between CK and slow TNNI1 (E) nor between fast TNNI2 and slow TNNI1 (F) In panels D – F, healthy samples are represented as black triangles, BMD as blue diamonds, and DMD red circles. ****: $p < 0.0001$. All other comparisons are nonsignificant.

[0309] Figure 4. Concentration of creatine kinase enzymatic activity (A), fast troponin I (TNNI2) (B), and slow troponin I (TNNI1) (C.) versus patient age in Duchenne muscular

dystrophy (DMD) patient samples. The same comparisons were made for Becker muscular dystrophy (BMD) in panels (D, E, and F) for CK, TNNI2, and TNNI1, respectively.

[0310] Figure 5. Ambulatory status for Duchenne muscular dystrophy (DMD) was compared against plasma concentrations of creatine kinase (CK) enzymatic activity (A), fast troponin I (TNNI2) (B), and slow troponin I (TNNI1) (C). The same comparisons were made for Becker muscular dystrophy (BMD) (D, E, and F). A patient was defined as “ambulatory” so long as the patient was not described as wholly dependent upon a wheelchair for mobility. Bars represent the mean $\pm$ the standard error for the population. ****: $p < 0.0001$, ns: non-significant.

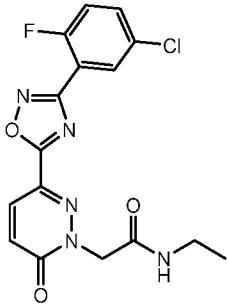
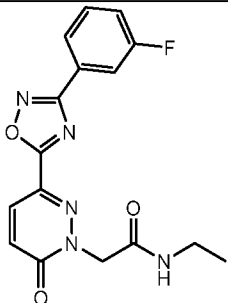
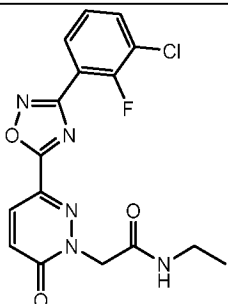
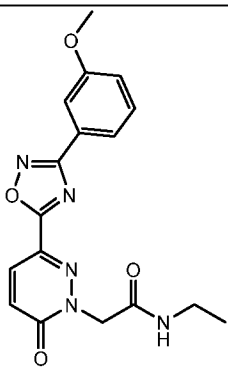
[0311] Figure 6. Plasma fast troponin I (A), myoglobin (B), and creatine kinase (C) in healthy control subjects (Controls), and in subjects with McArdle disease (McA) or Becker muscular dystrophy (BMD) after exercise. Data are expressed as mean $\pm$ SE. X-axis: 0 = before exercise, and 1, 2, 4, 24, and 48 = hours after completed exercise. Asterisk indicates significant ($P < 0.05$) difference compared with pre-exercise. N = 6 (McArdles), 4 (BMD), and 11 (healthy volunteers).

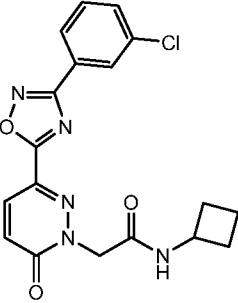
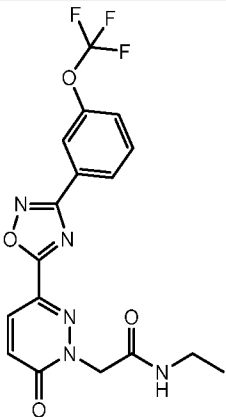
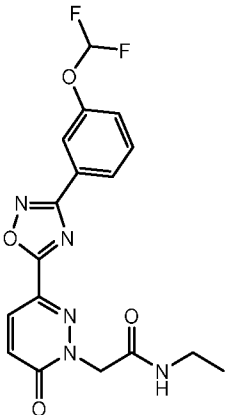
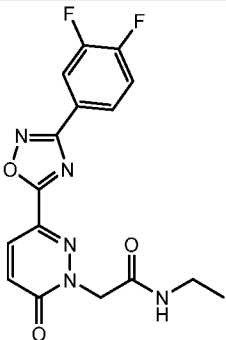
[0312] Figure 7. Comparison of levels of creatine kinase (CK) pre and post exercise in healthy adults and subjects with BMD, LGMD, and McArdle’s disease. Data are expressed as mean $\pm$ SE. X-axis: 0 = before exercise, and 1, 2, 4, and 24 = hours after completed exercise. Note that the assay maxes out at 22,000 U/L, which is relevant to the McArdle data.

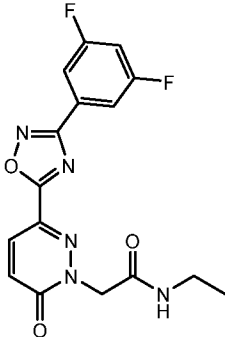
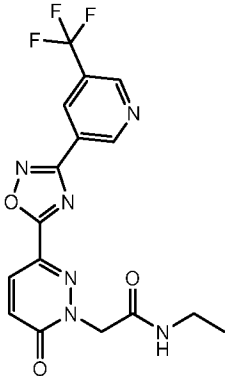
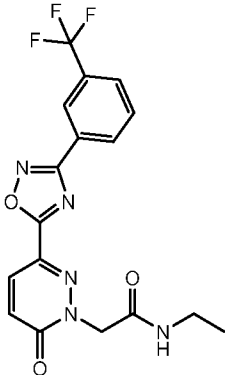
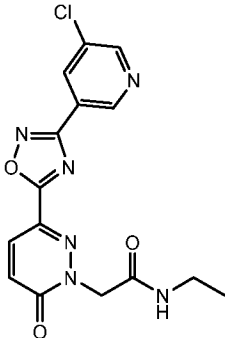
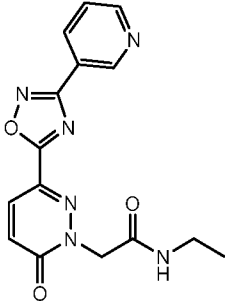
[0313] Figure 8. Comparison of levels of myoglobin pre and post exercise in healthy adults and subjects with BMD, LGMD, and McArdle’s disease. Data are expressed as mean $\pm$ SE. X-axis: 0 = before exercise, and 1, 2, 4, and 24 = hours after completed exercise.

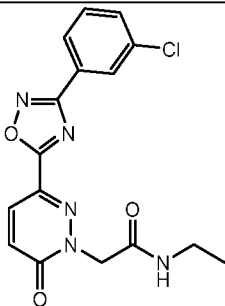
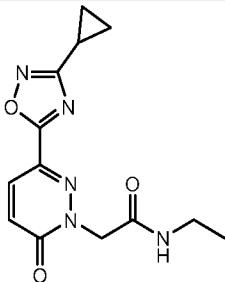
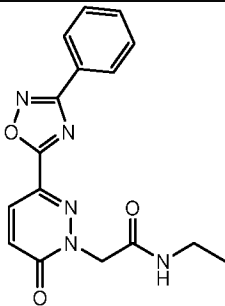
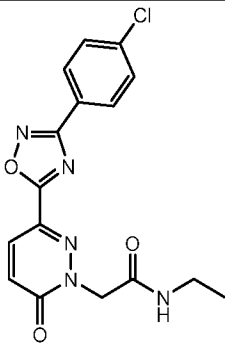
[0314] In some embodiments, compounds of the disclosure are below in Table 1.

TABLE 1

Compound No	ChemDraw	Chem Name
1		2-(3-(3-(5-chloro-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
2		N-ethyl-2-(3-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)acetamide
3		2-(3-(3-(3-chloro-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
4		N-ethyl-2-(3-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)acetamide

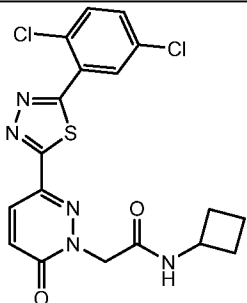
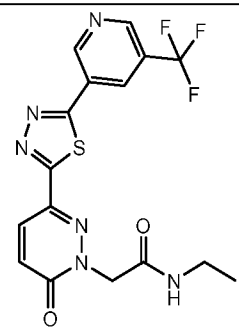
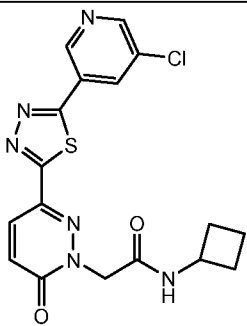
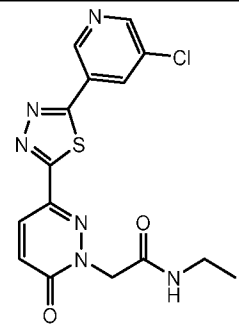
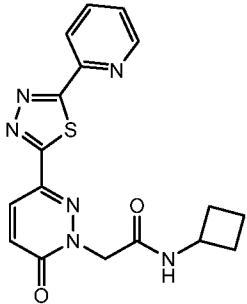
5		2-(3-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-cyclobutylacetamide
6		N-ethyl-2-(6-oxo-3-(3-(3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)acetamide
7		2-(3-(3-(3-(difluoromethoxy)phenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
8		2-(3-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide

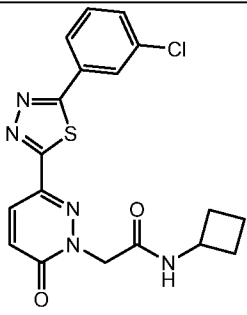
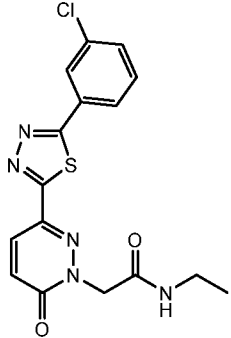
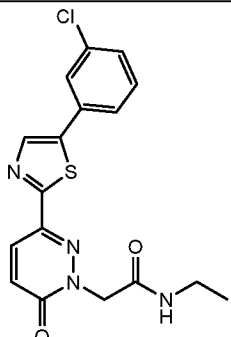
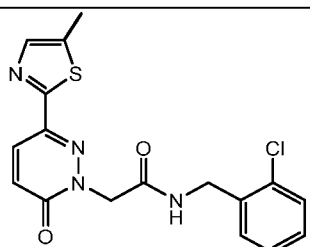
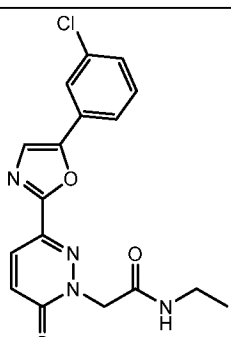
9		2-(3-(3-(3,5-difluorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
10		N-ethyl-2-(6-oxo-3-(3-(5-(trifluoromethyl)pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)acetamide
11		N-ethyl-2-(6-oxo-3-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)acetamide
12		2-(3-(3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
13		N-ethyl-2-(6-oxo-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)acetamide

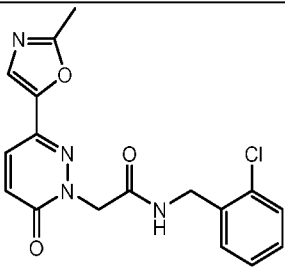
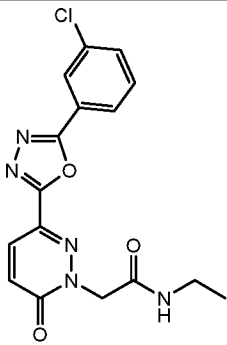
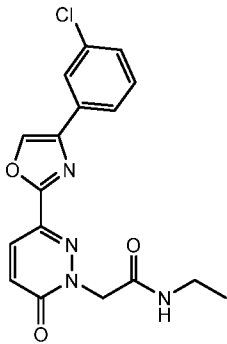
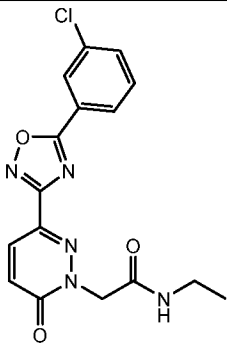
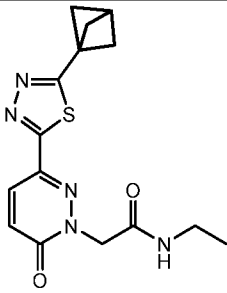
14		2-(3-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
15		2-(3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
16		N-ethyl-2-(6-oxo-3-(3-phenyl-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)acetamide
17		2-(3-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide

[0315] In some embodiments, compounds of the disclosure are below in Table 2.

TABLE 2

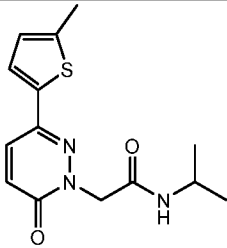
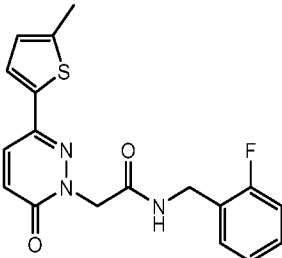
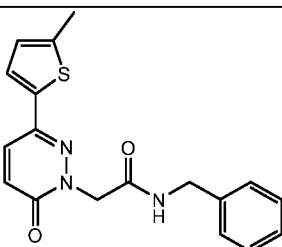
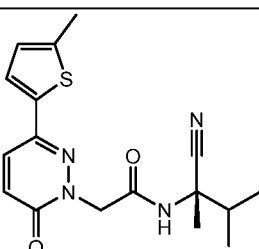
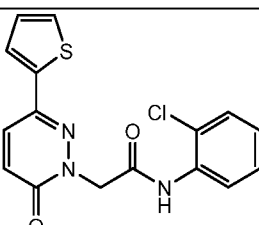
Compound No	ChemDraw	Chem Name
18		N-cyclobutyl-2-(3-(5-(2,5-dichlorophenyl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
19		N-ethyl-2-(6-oxo-3-(5-(5-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)pyridazin-1(6H)-yl)acetamide
20		2-(3-(5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-cyclobutylacetamide
21		2-(3-(5-(5-chloropyridin-3-yl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
22		N-cyclobutyl-2-(6-oxo-3-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)pyridazin-1(6H)-yl)acetamide

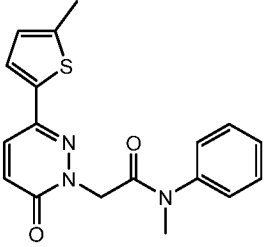
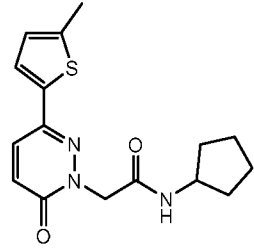
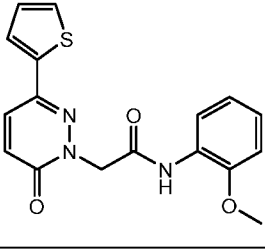
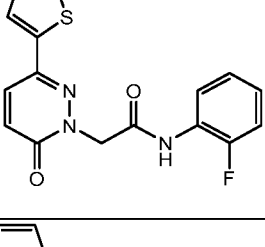
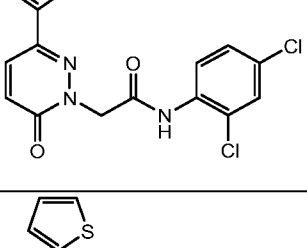
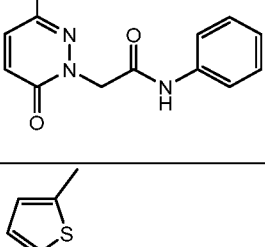
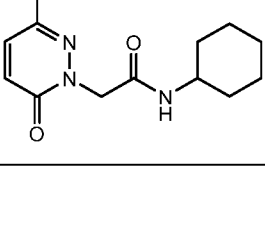
23		2-(3-(5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-cyclobutylacetamide
24		2-(3-(5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
25		2-(3-(5-(3-chlorophenyl)thiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
26		N-(2-chlorobenzyl)-2-(3-(5-methylthiazol-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
27		2-(3-(5-(3-chlorophenyl)oxazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide

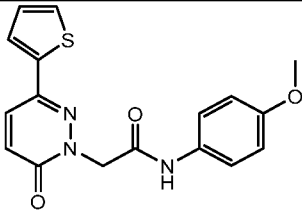
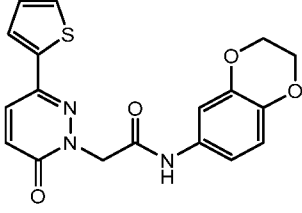
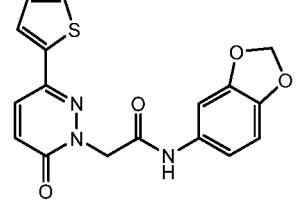
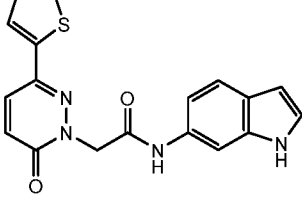
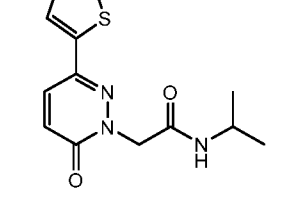
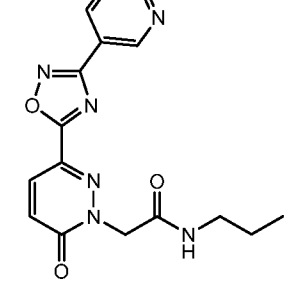
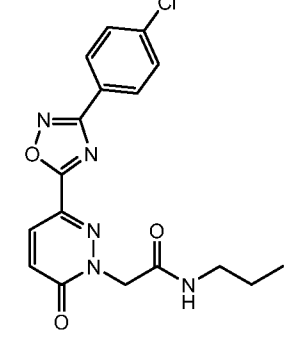
28		N-(2-chlorobenzyl)-2-(3-(2-methyloxazol-5-yl)-6-oxopyridazin-1(6H)-yl)acetamide
29		2-(3-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
30		2-(3-(4-(3-chlorophenyl)oxazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
31		2-(3-(5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
32		2-(3-(5-(bicyclo[1.1.1]pentan-1-yl)-1,3,4-thiadiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide

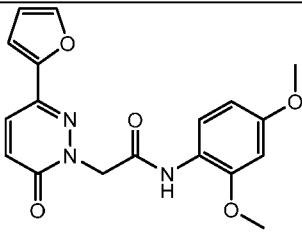
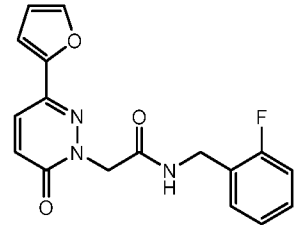
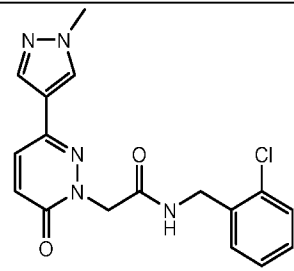
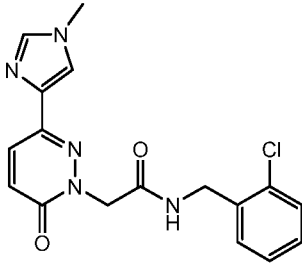
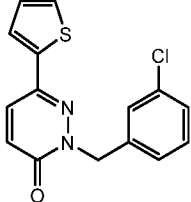
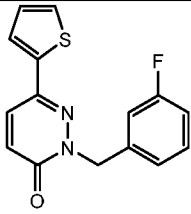
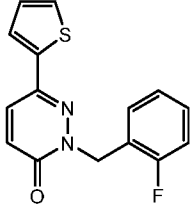
[0316] In certain embodiments, compounds of the methods described herein may be selected from commercially available compounds including those described in Table 3. Compounds of Table 3 were tested and IC₅₀ data appears in Table 4 herein. A = IC₅₀ is less than or equal to 10 μ M; B = IC₅₀ is greater than 10 μ M and less than 100 μ M; C = IC₅₀ is greater than 100 μ M.

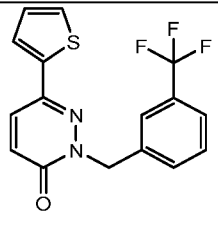
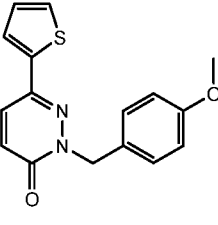
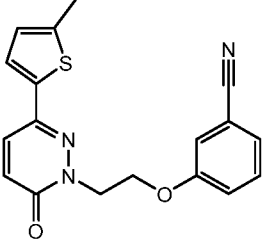
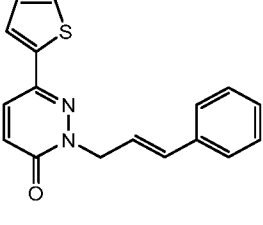
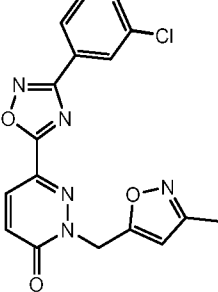
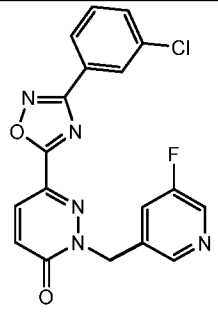
TABLE 3

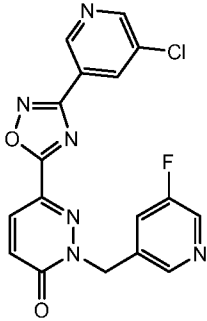
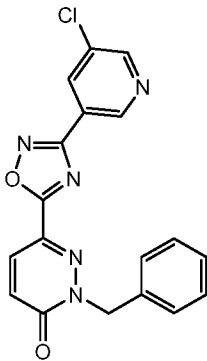
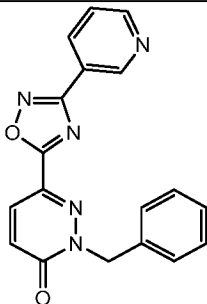
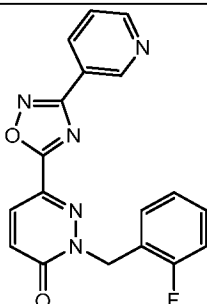
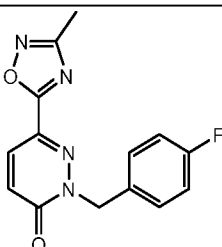
Compound No	ChemDraw	Chem Name
33		N-isopropyl-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
34		N-(2-fluorobenzyl)-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
35		N-benzyl-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
36		(S)-N-(2-cyano-3-methylbutan-2-yl)-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
37		N-(2-chlorophenyl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide

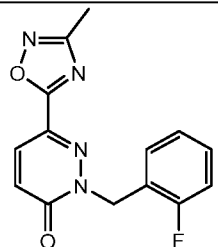
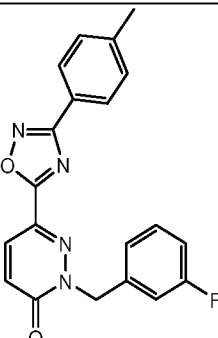
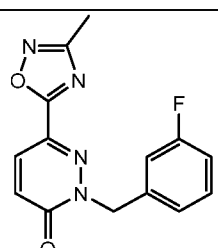
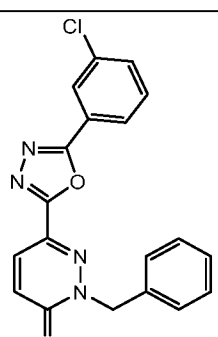
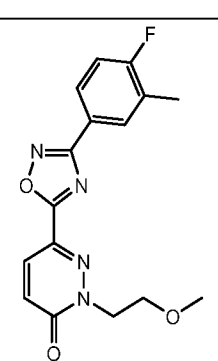
38		N-methyl-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)-N-phenylacetamide
39		N-cyclopentyl-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
40		N-(2-methoxyphenyl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
41		N-(2-fluorophenyl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
42		N-(2,4-dichlorophenyl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
43		2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)-N-phenylacetamide
44		N-cyclohexyl-2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide

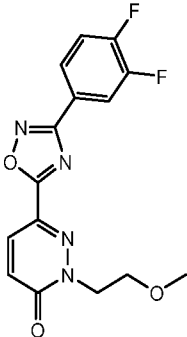
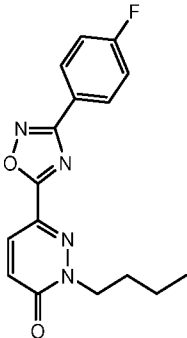
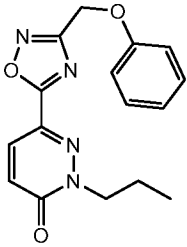
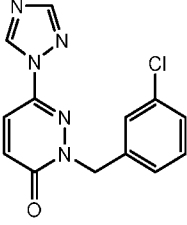
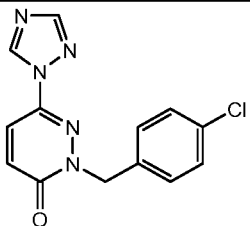
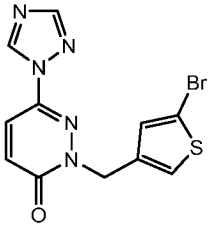
45		N-(4-methoxyphenyl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
46		N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
47		N-(benzo[d][1,3]dioxol-5-yl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
48		N-(1H-indol-6-yl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
49		N-isopropyl-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
50		2-(6-oxo-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-1(6H)-yl)-N-propylacetamide
51		2-(3-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-6-oxopyridazin-1(6H)-yl)-N-propylacetamide

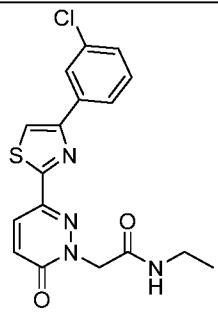
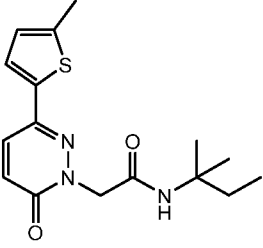
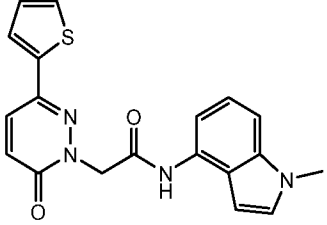
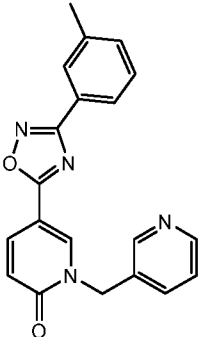
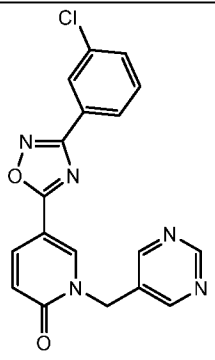
52		N-(2,4-dimethoxyphenyl)-2-(3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
53		N-(2-fluorobenzyl)-2-(3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl)acetamide
54		N-(2-chlorobenzyl)-2-(3-(1-methyl-1H-pyrazol-4-yl)-6-oxopyridazin-1(6H)-yl)acetamide
55		N-(2-chlorobenzyl)-2-(3-(1-methyl-1H-imidazol-4-yl)-6-oxopyridazin-1(6H)-yl)acetamide
56		2-(3-chlorobenzyl)-6-(thiophen-2-yl)pyridazin-3(2H)-one
57		2-(3-fluorobenzyl)-6-(thiophen-2-yl)pyridazin-3(2H)-one
58		2-(2-fluorobenzyl)-6-(thiophen-2-yl)pyridazin-3(2H)-one

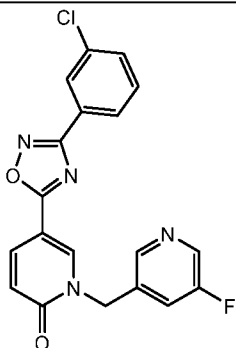
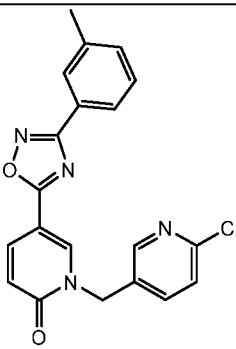
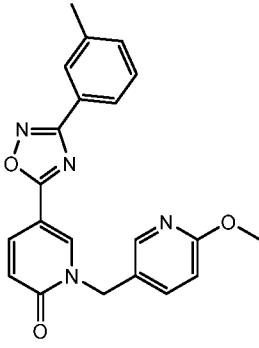
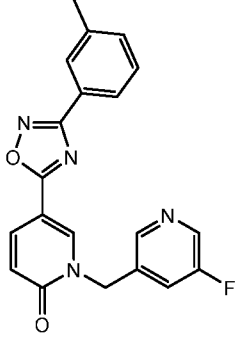
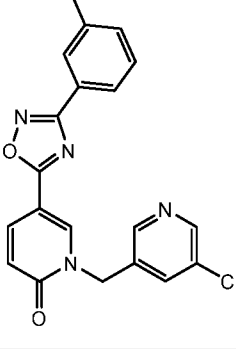
59		6-(thiophen-2-yl)-2-(3-(trifluoromethyl)benzyl)pyridazin-3(2H)-one
60		2-(4-methoxybenzyl)-6-(thiophen-2-yl)pyridazin-3(2H)-one
61		3-(2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)ethoxy)benzonitrile
62		2-cinnamyl-6-(thiophen-2-yl)pyridazin-3(2H)-one
63		6-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-2-((3-methylisoxazol-5-yl)methyl)pyridazin-3(2H)-one
64		6-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-2-((5-fluoropyridin-3-yl)methyl)pyridazin-3(2H)-one

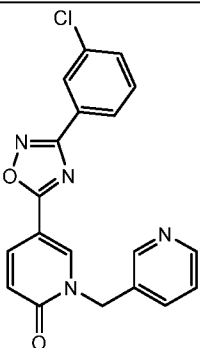
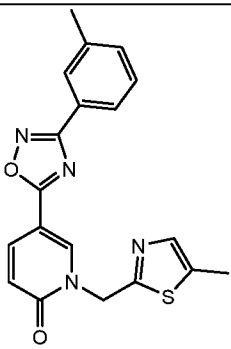
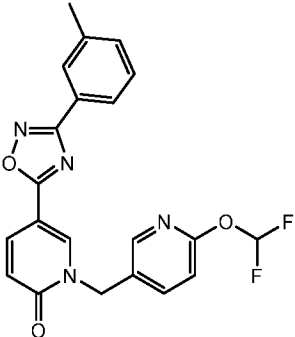
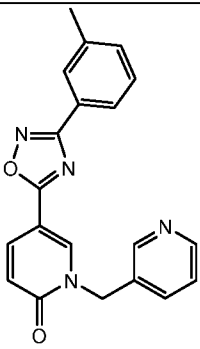
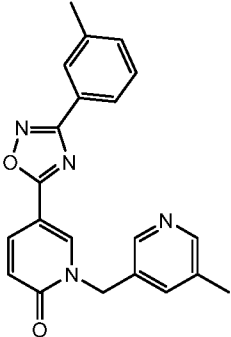
65		6-(3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)-2-((5-fluoropyridin-3-yl)methyl)pyridazin-3(2H)-one
66		2-benzyl-6-(3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
67		2-benzyl-6-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
68		2-(2-fluorobenzyl)-6-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
69		2-(4-fluorobenzyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one

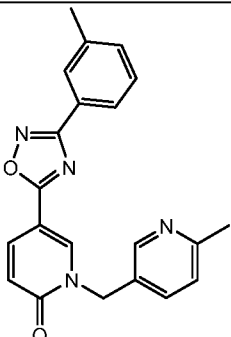
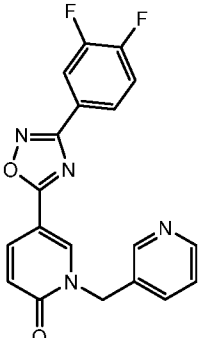
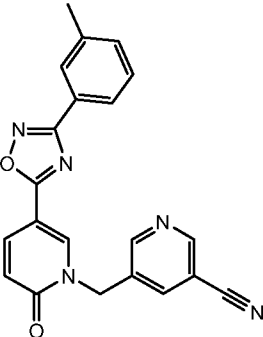
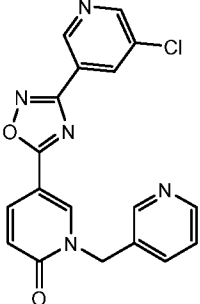
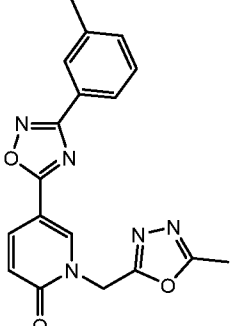
70		2-(2-fluorobenzyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
71		2-(3-fluorobenzyl)-6-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
72		2-(3-fluorobenzyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
73		2-benzyl-6-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)pyridazin-3(2H)-one
74		6-(3-(4-fluoro-3-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-(2-methoxyethyl)pyridazin-3(2H)-one

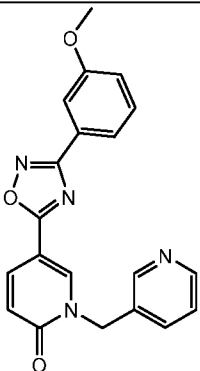
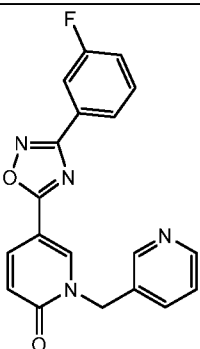
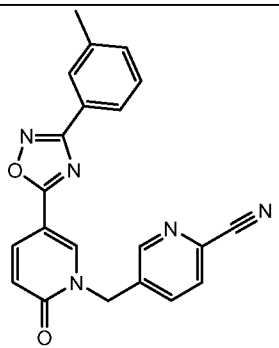
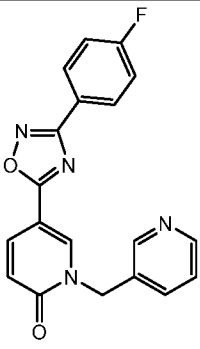
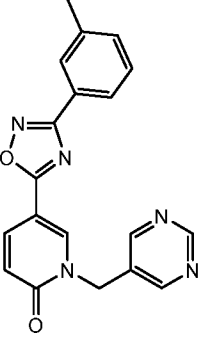
75		6-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)-2-(2-methoxyethyl)pyridazin-3(2H)-one
76		2-butyl-6-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)pyridazin-3(2H)-one
77		6-(3-(phenoxymethyl)-1,2,4-oxadiazol-5-yl)-2-propylpyridazin-3(2H)-one
78		2-(3-chlorobenzyl)-6-(1H-1,2,4-triazol-1-yl)pyridazin-3(2H)-one
79		2-(4-chlorobenzyl)-6-(1H-1,2,4-triazol-1-yl)pyridazin-3(2H)-one
80		2-((5-bromothiophen-3-yl)methyl)-6-(1H-1,2,4-triazol-1-yl)pyridazin-3(2H)-one

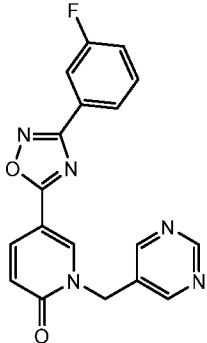
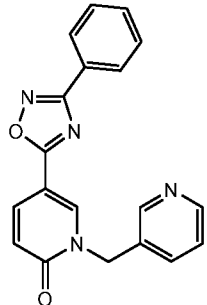
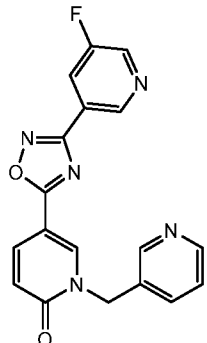
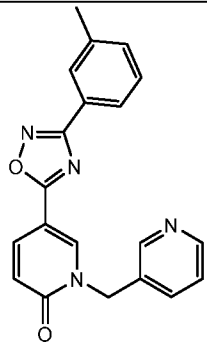
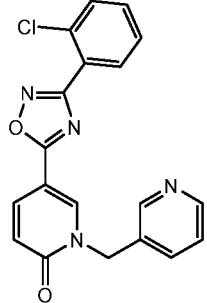
81		2-(3-(4-(3-chlorophenyl)thiazol-2-yl)-6-oxopyridazin-1(6H)-yl)-N-ethylacetamide
82		2-(3-(5-methylthiophen-2-yl)-6-oxopyridazin-1(6H)-yl)-N-(tert-pentyl)acetamide
83		N-(1-methyl-1H-indol-4-yl)-2-(6-oxo-3-(thiophen-2-yl)pyridazin-1(6H)-yl)acetamide
84		1-(pyridin-3-ylmethyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
85		5-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyrimidin-5-ylmethyl)pyridin-2(1H)-one

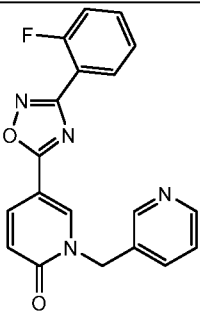
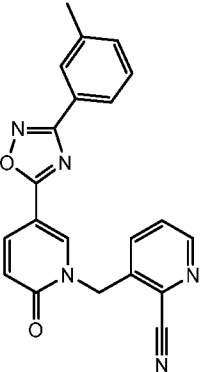
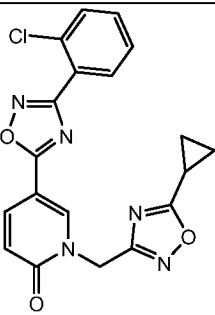
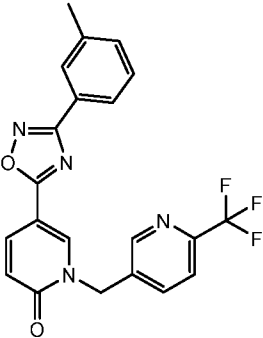
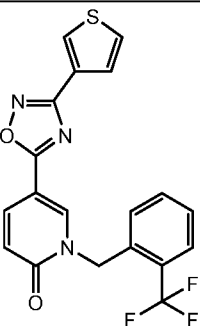
86		5-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-((5-fluoropyridin-3-yl)methyl)pyridin-2(1H)-one
87		1-((6-chloropyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
88		1-((6-methoxypyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
89		1-((5-fluoropyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
90		1-((5-chloropyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one

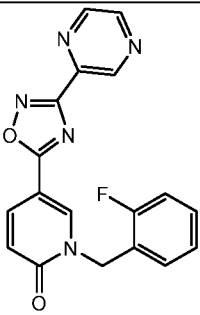
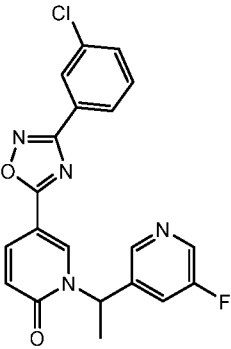
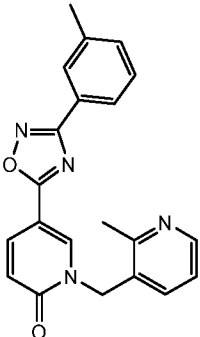
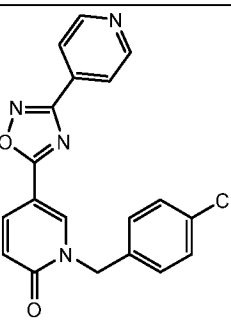
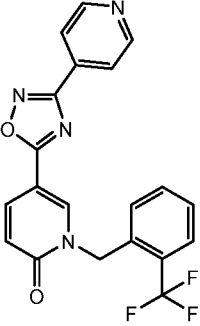
91		5-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
92		1-((5-methylthiazol-2-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
93		1-((6-(difluoromethoxy)pyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
94		1-(pyridin-3-ylmethyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
95		1-((5-methylpyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one

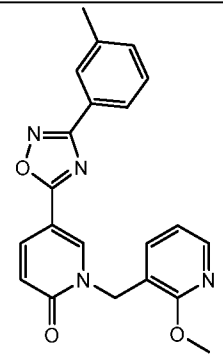
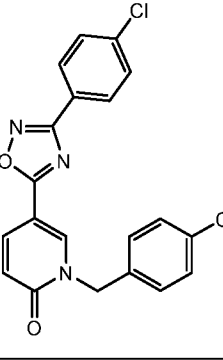
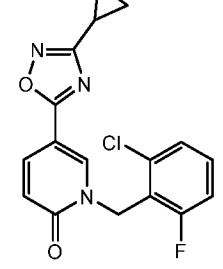
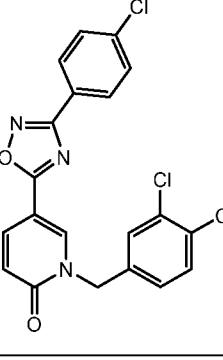
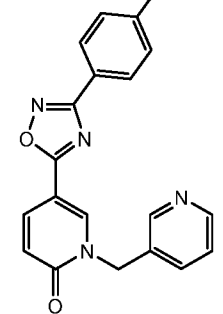
96		1-((6-methylpyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
97		5-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
98		5-((2-oxo-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-1(2H)-yl)methyl)nicotinonitrile
99		5-(3-(5-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
100		1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one

101		5-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
102		5-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
103		5-((2-oxo-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-1(2H)-yl)methyl)picolinonitrile
104		5-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
105		1-(pyrimidin-5-ylmethyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one

106		5-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyrimidin-5-ylmethyl)pyridin-2(1H)-one
107		5-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
108		5-(3-(5-fluoropyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
109		1-(pyridin-3-ylmethyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
110		5-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

111		5-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one
112		3-((2-oxo-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-1(2H)-yl)methyl)picolinonitrile
113		5-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)pyridin-2(1H)-one
114		5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)pyridin-2(1H)-one
115		5-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)-1-(2-(trifluoromethyl)benzyl)pyridin-2(1H)-one

116		1-(2-fluorobenzyl)-5-(3-(pyrazin-2-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
117		5-(3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(1-(5-fluoropyridin-3-yl)ethyl)pyridin-2(1H)-one
118		1-((2-methylpyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
119		1-(4-chlorobenzyl)-5-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
120		5-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)-1-(2-(trifluoromethyl)benzyl)pyridin-2(1H)-one

121		1-((2-methoxypyridin-3-yl)methyl)-5-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
122		1-(4-chlorobenzyl)-5-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
123		1-(2-chloro-6-fluorobenzyl)-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one
124		5-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(3,4-dichlorobenzyl)pyridin-2(1H)-one
125		5-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

[0317] Skeletal IC₅₀ values of compounds of the disclosure appear in Table 4.

TABLE 4

Cmpd No.	IC₅₀	Cmpd No.	IC₅₀	Cmpd No.	IC₅₀
1	A	11	A	22	A
2	A	12	A	23	A
3	A	13	B	24	A
4	A	14	A	25	A
5	A	15	B	26	A
6	A	16	A	27	A
7	A	17	A	28	B
8	A	18	A	30	A
9	A	19	A	31	A
10	A	20	A	32	A
33	A	43	C	53	C
34	A	44	C	54	B
35	B	45	B	55	C
36	B	46	C	56	A
37	B	47	C	57	B
38	B	48	C	58	C
39	B	49	C	59	C
40	B	50	B	60	C
41	B	51	A	61	C
42	C	52	B	62	C
63	A	73	A	83	A
64	A	74	B	84	A
65	A	75	B	85	A
66	A	76	A	86	A
67	B	77	B	87	A
68	B	78	B	88	A

Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀
69	B	79	B	89	A
70	B	80	B	90	A
71	C	81	C	91	A
72	B	82	A	92	A
93	A	103	A	113	D
94	A	104	A	114	D
95	A	105	A	115	D
96	A	106	A	116	D
97	A	107	B	117	D
98	A	108	B	118	D
99	A	109	B	119	D
100	A	110	B	120	D
101	A	111	D	121	D
102	A	112	D	122	D
123	D				
124	D				
125	D				

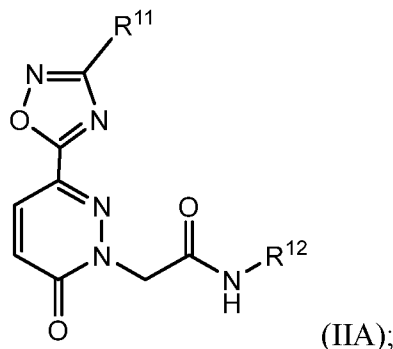
A = IC₅₀ is less than or equal to 10 μ M; B = IC₅₀ is greater than 10 μ M and less than 100 μ M; C = IC₅₀ is greater than 100 μ M; D = IC₅₀ greater than 120 μ M.

[0318] 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 methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (IIA):



or a salt thereof, wherein:

R^{11} is selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, $-CN$, 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^{15} ; 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, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl are optionally substituted with one or more substituents independently selected from R^{17} and C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more substituents independently selected from R^{15} ;

R^{12} is selected from: cyclobutyl optionally substituted with one or more substituents independently selected from R^{15} ; and ethyl optionally substituted with one or more substituents independently selected from R^{17} ;

each R^{15} is independently selected from:

halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, 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, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, and $-CN$;

each R^{16} is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, 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;

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; and

each R^{17} is independently selected from halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, and $-CN$.

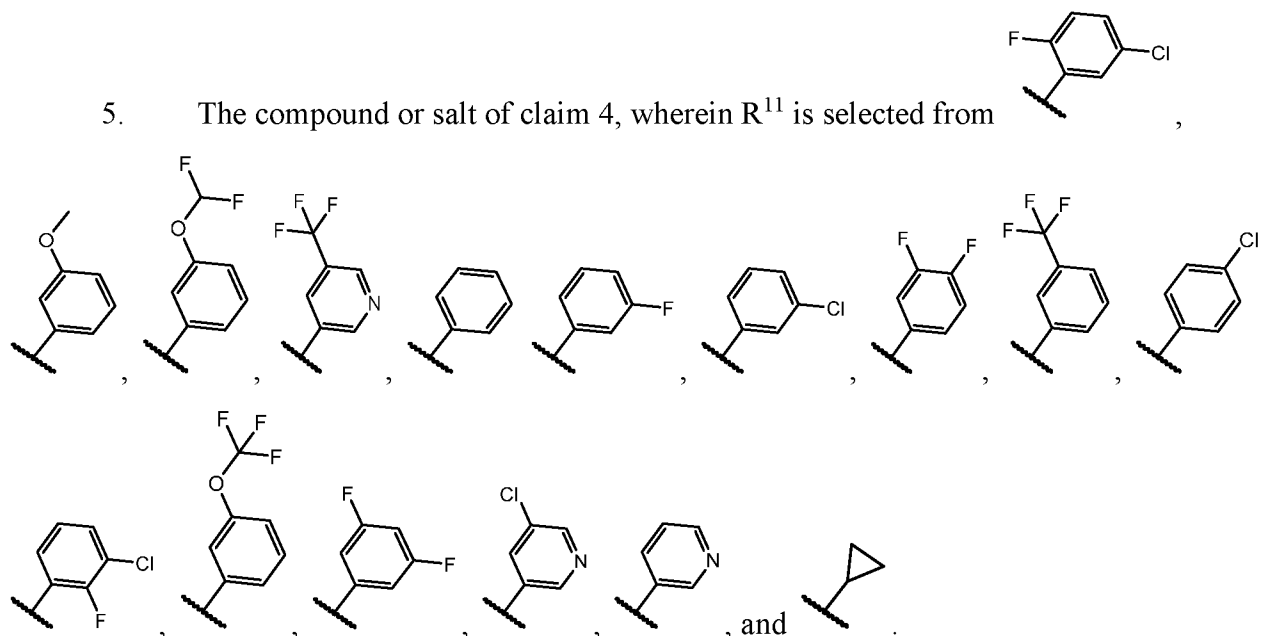
2. The compound or salt of claim 1, wherein R^{11} is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-SR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)N(R^{16})_2$, $-N(R^{16})C(O)OR^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-NO_2$, $=O$, $=S$, $=N(R^{16})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{15} .

3. The compound or salt of claim 2, wherein R^{11} is selected from cycloalkyl, aryl and heteroaryl, each of which is optionally substituted with one or more substituents independently selected from R^{15} .

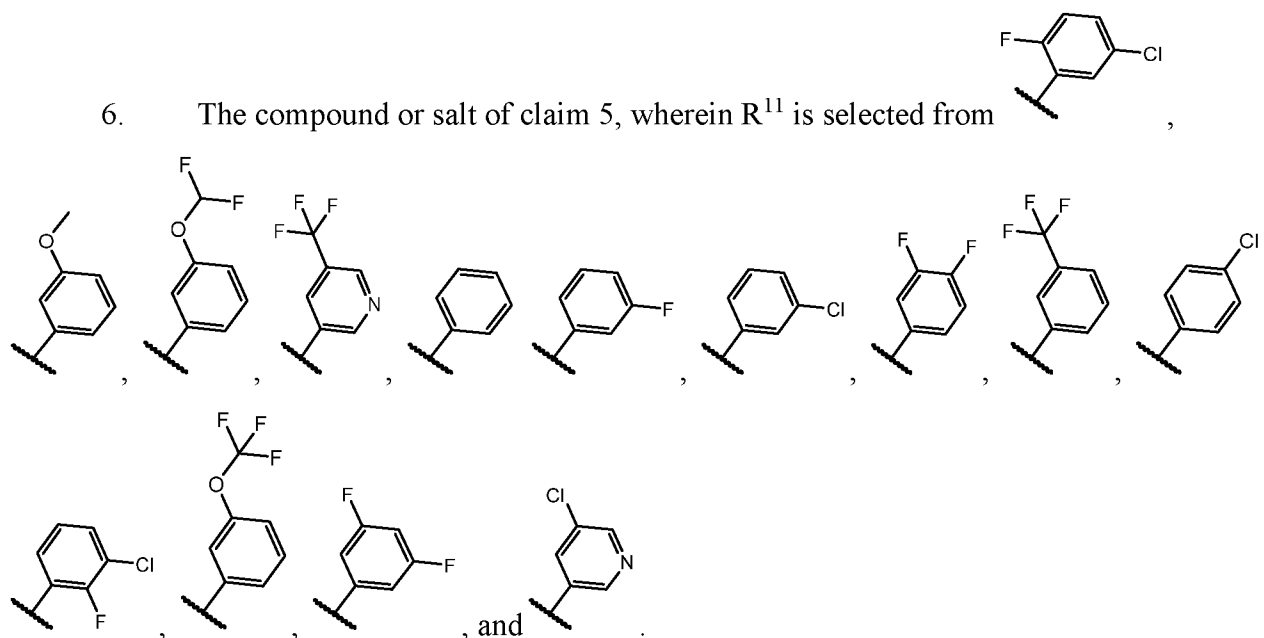
4. The compound or salt of claim 3, wherein R^{11} is selected from phenyl, pyridyl, and cyclopropyl, each of which is optionally substituted with one or more substituents independently

selected from halogen, $-OR^{16}$, and C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen.

5. The compound or salt of claim 4, wherein R^{11} is selected from



6. The compound or salt of claim 5, wherein R^{11} is selected from



7. The compound of any one of claims 1 to 6, wherein R^{12} is cyclobutyl optionally substituted with one or more substituents independently selected from:

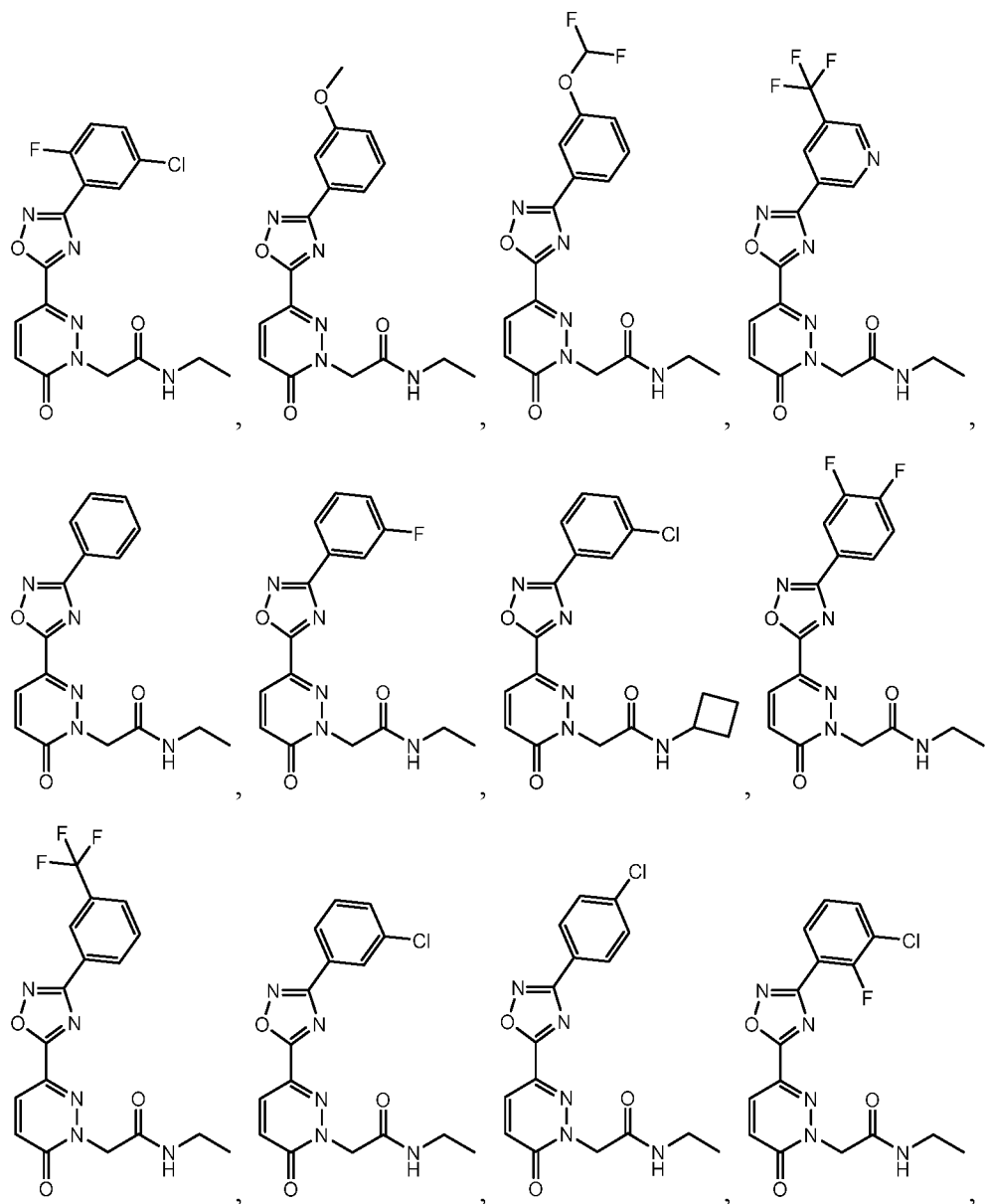
halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NO_2$, and $-CN$; and

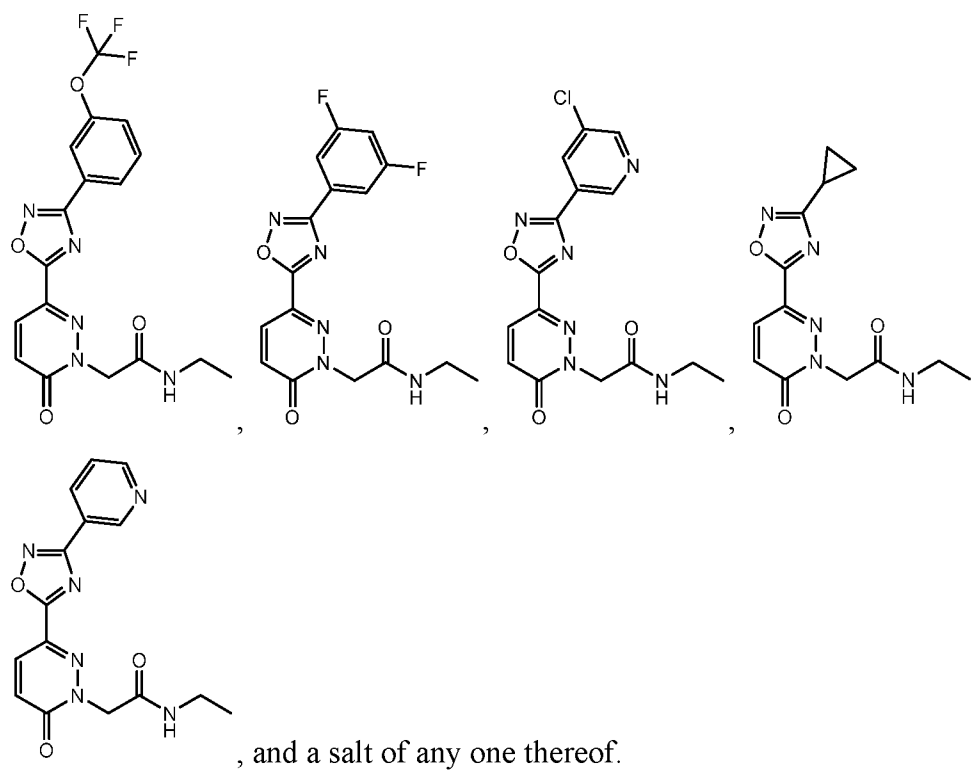
C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NO_2$, and $-CN$.

8. The compound of any one of claims 1 to 6, wherein R^{12} is ethyl optionally substituted with halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)N(R^{16})_2$, $-N(R^{16})C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NO_2$, and $-CN$.

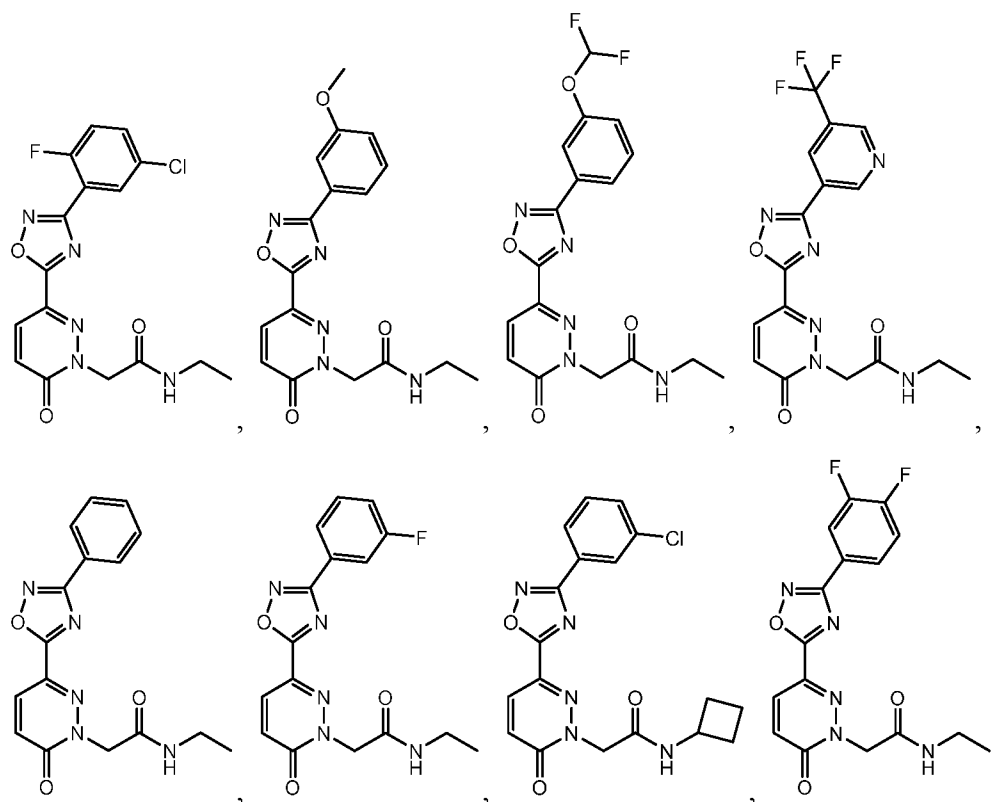
9. The compound of any one of claims 1 to 6, wherein R^{12} is ethyl or cyclobutyl.

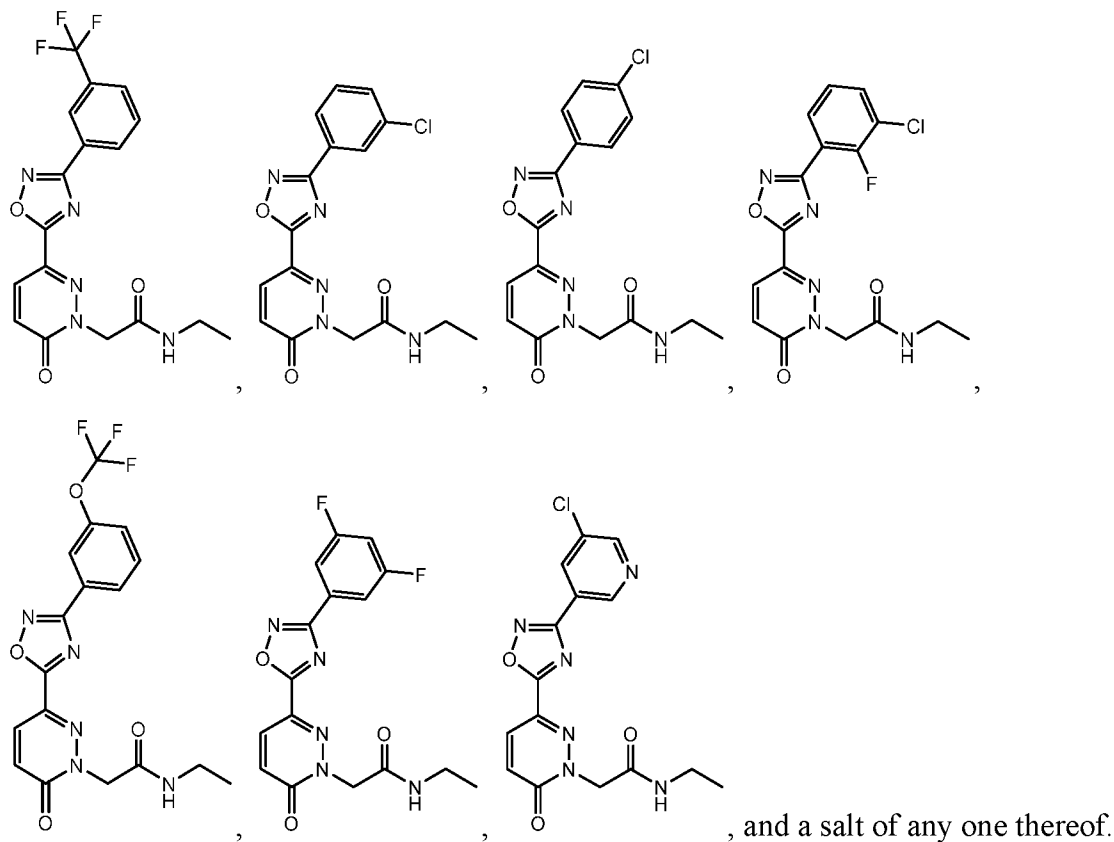
10. The compound of claim 1, wherein the compound is selected from:



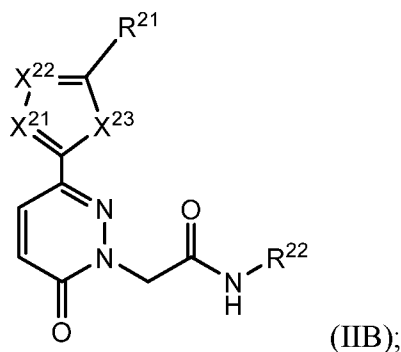


11. The compound of claim 1, wherein the compound is selected from:





12. A compound represented by Formula (IIB):



or a salt thereof, wherein:

X^{21} and X^{22} are independently selected from N and C(R²³), wherein at least one of X^{21} and X^{22} is N;

X^{23} is selected from S and O;

R^{21} is selected from:

hydrogen;

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR²⁶, -SR²⁶, -N(R²⁶)₂, -C(O)R²⁶, -C(O)N(R²⁶)₂, -N(R²⁶)C(O)R²⁶, -C(O)OR²⁶, -OC(O)R²⁶, -N(R²⁶)C(O)N(R²⁶)₂, -OC(O)N(R²⁶)₂, -N(R²⁶)C(O)OR²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -NO₂, =O, =S, =N(R²⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀

carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} ; 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, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} ;

R^{22} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, 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^{25} ; 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, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-N(R^{26})C(O)N(R^{26})_2$, $-OC(O)N(R^{26})_2$, $-N(R^{26})C(O)OR^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-NO_2$, $=O$, $=S$, $=N(R^{26})$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} ;

R^{23} is selected from:

hydrogen;

halogen, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$ and $-CN$; and

C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-SR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, and $-CN$;

each R^{25} is independently selected from:

halogen, $-\text{OR}^{26}$, $-\text{SR}^{26}$, $-\text{N}(\text{R}^{26})_2$, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{R}^{26}$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{OR}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{OC}(\text{O})\text{R}^{26}$, $-\text{S}(\text{O})\text{R}^{26}$, $-\text{S}(\text{O})_2\text{R}^{26}$, $-\text{NO}_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{26})$, $-\text{CN}$; 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, $-\text{OR}^{26}$, $-\text{SR}^{26}$, $-\text{N}(\text{R}^{26})_2$, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{R}^{26}$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{OR}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{OC}(\text{O})\text{R}^{26}$, $-\text{S}(\text{O})\text{R}^{26}$, $-\text{S}(\text{O})_2\text{R}^{26}$, $-\text{NO}_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{26})$, and $-\text{CN}$;

each R^{26} is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-\text{CN}$, $-\text{OH}$, $-\text{SH}$, $-\text{NO}_2$, $-\text{NH}_2$, $=\text{O}$, $=\text{S}$, $-\text{O}-\text{C}_{1-6}$ alkyl, $-\text{S}-\text{C}_{1-6}$ alkyl, $-\text{N}(\text{C}_{1-6}$ alkyl) $_2$, $-\text{NH}(\text{C}_{1-6}$ alkyl), C_{3-10} carbocycle, 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, $-\text{CN}$, $-\text{OH}$, $-\text{SH}$, $-\text{NO}_2$, $-\text{NH}_2$, $=\text{O}$, $=\text{S}$, $-\text{O}-\text{C}_{1-6}$ alkyl, $-\text{S}-\text{C}_{1-6}$ alkyl, $-\text{N}(\text{C}_{1-6}$ alkyl) $_2$, $-\text{NH}(\text{C}_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and haloalkyl.

13. The compound or salt of claim 12, wherein X^{23} is O.

14. The compound or salt of claim 12, wherein X^{23} is S.

15. The compound or salt of any one of claims 12, 13, or 14, wherein X^{21} is N and X^{22} is CR^{23} or X^{22} is N and X^{21} is CR^{23} .

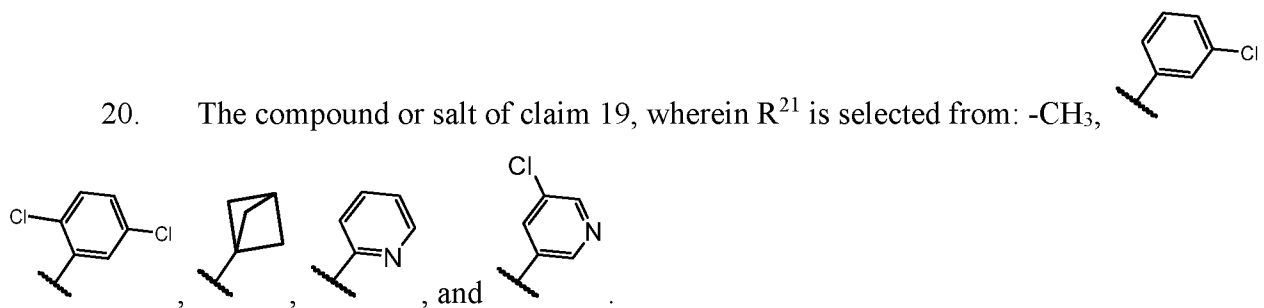
16. The compound or salt of any one of claims 12, 13, 14, or 15, wherein CR^{23} is CH.

17. The compound or salt of any one of claims 12, 13, or 14, wherein X^{21} and X^{22} are each N.

18. The compound or salt of any one of claims 12 to 17, wherein R^{21} is selected from optionally substituted C_{1-6} alkyl, optionally substituted aryl, and optionally substituted heteroaryl.

19. The compound or salt of claim 18, wherein R^{21} is selected from optionally substituted C_{1-3} alkyl, optionally substituted C_{3-6} carbocycle, and optionally substituted 5- or 6-membered heteroaryl; wherein substituents on C_{1-3} alkyl are selected from halogen, $-\text{OR}^{26}$, $-\text{N}(\text{R}^{26})_2$, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{OC}(\text{O})\text{R}^{26}$, $-\text{NO}_2$, and $-\text{CN}$, and substituents on C_{3-6} carbocycle and 5- or 6-membered heteroaryl are selected from halogen, $-\text{OR}^{26}$, $-\text{N}(\text{R}^{26})_2$, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})_2$, $-\text{N}(\text{R}^{26})\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{OC}(\text{O})\text{R}^{26}$, $-\text{NO}_2$, and $-\text{CN}$.

$C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, and C_{1-6} alkyl optionally substituted with one or more R^{25} .



21. The compound of any one of claims 12 to 20, wherein R^{22} is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, 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^{25} ; and

C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from: halogen, $-OR^{26}$, $-N(R^{26})_2$, $-C(O)R^{26}$, $-C(O)N(R^{26})_2$, $-N(R^{26})C(O)R^{26}$, $-C(O)OR^{26}$, $-OC(O)R^{26}$, $-NO_2$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} .

22. The compound of claim 21, wherein R^{22} is selected from:

C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more R^{25} ; and

C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from: halogen, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{25} .

23. The compound of claim 22, wherein R^{22} is selected from:

C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, and phenyl optionally substituted with one or more substituents independently selected from halogen; and

C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from: halogen, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

$N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, 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^{35} ; 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{35} ;

R^{32} is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, 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^{35} ; 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^{35} ;

each R^{35} is independently selected from:

halogen, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$, $-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, 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, $-OR^{36}$, $-SR^{36}$, $-N(R^{36})_2$, $-C(O)R^{36}$, $-C(O)N(R^{36})_2$, $-N(R^{36})C(O)R^{36}$, $-N(R^{36})C(O)N(R^{36})_2$, $-OC(O)N(R^{36})_2$,

$-N(R^{36})C(O)OR^{36}$, $-C(O)OR^{36}$, $-OC(O)R^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-NO_2$, $=O$, $=S$, $=N(R^{36})$, and $-CN$;

each R^{36} is independently selected from:

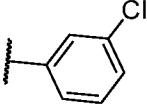
hydrogen;

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

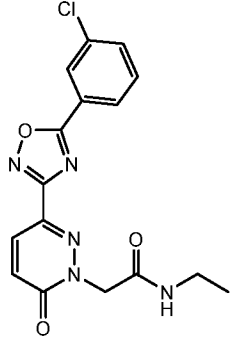
27. The compound or salt of claim 26, wherein R^{31} is selected from optionally substituted aryl or heteroaryl.

28. The compound or salt of claim 27, wherein R^{31} is selected from optionally substituted phenyl.

29. The compound or salt of claim 28, wherein R^{31} is .

30. The compound or salt of any one of claims 26, 27 or 28, wherein R^{32} is selected from optionally substituted C_1 - C_6 alkyl.

31. The compound or salt of claim 30, wherein R^{32} is ethyl.

32. The compound of claim 26, wherein the compound is , or a salt thereof.

33. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 32.

34. A method of treating disease, comprising administering to a subject in need thereof a compound or salt of any one of claims 1 to 32.

35. A method of treating a neuromuscular condition, comprising administering to a subject in need thereof a compound or salt of any one of claims 1 to 32.

36. The method of claim 34 or 35, 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, carpal tunnel syndrome.

37. The method of claim 36, wherein said neuromuscular condition is Duchenne Muscular Dystrophy.

38. A method of treating a movement disorder, comprising administering to a subject in need thereof a compound or salt of any one of claims 1 to 32.

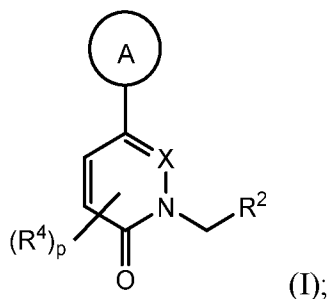
39. The method of claim 38, wherein the movement disorder comprises muscle spasticity.

40. The method of claim 39, wherein the muscle spasticity is selected from spasticity associated with multiple sclerosis, Parkinson's disease, Alzheimer's disease, or cerebral palsy, or injury, or a traumatic event such as stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, or amyotrophic lateral sclerosis.

41. The method of claim 40, wherein the compound or salt is administered in an amount sufficient to reduce involuntary muscle contractions.

42. The method of claim 41, wherein the compound or salt is administered in an amount sufficient to reduce involuntary muscle contractions by at least 10%.

43. A method of treating a neuromuscular condition or movement disorder, comprising administering to a subject in need thereof a compound represented by Formula (I):



or a salt thereof, wherein:

the A ring is selected from a 5-membered heteroaromatic ring optionally substituted by one or more substituents independently selected from R¹;

X is N or CH;

each R¹ is independently selected from:

halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, and $-CN$;

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, 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^5 ; 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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ;

R^2 is selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, $-CN$, 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^5 ;

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, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-C(O)N(R^6)_2$, $-N(R^6)C(O)R^6$, $-N(R^6)C(O)N(R^6)_2$, $-OC(O)N(R^6)_2$, $-N(R^6)C(O)OR^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-NO_2$, $=O$, $=S$, $=N(R^6)$, and $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ; and

$-C(O)NR^7R^8$;

each R^4 is independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-NO_2$, $-CN$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-NO_2$, and $-CN$;

each R⁵ is independently selected from:

halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN; and

C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), and -CN;

each R⁶ is independently selected from:

hydrogen; and

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

C₃₋₁₀ 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, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and haloalkyl;

R⁷ is selected from hydrogen and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -NO₂, and -CN;

R⁸ is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

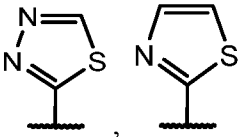
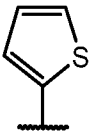
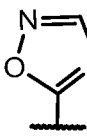
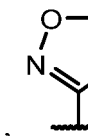
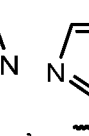
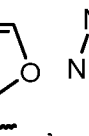
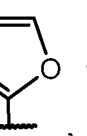
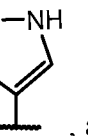
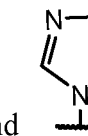
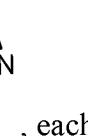
C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -C(O)R⁶, -C(O)N(R⁶)₂, -N(R⁶)C(O)R⁶, -N(R⁶)C(O)N(R⁶)₂, -OC(O)N(R⁶)₂, -N(R⁶)C(O)OR⁶, -C(O)OR⁶, -OC(O)R⁶, -S(O)R⁶, -S(O)₂R⁶, -NO₂, =O, =S, =N(R⁶), -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀

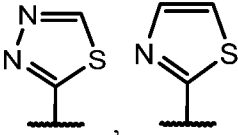
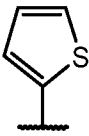
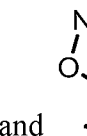
carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 ; and

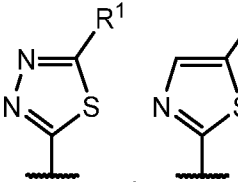
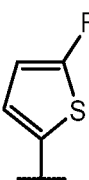
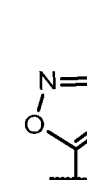
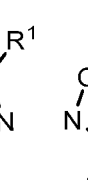
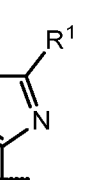
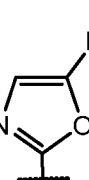
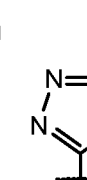
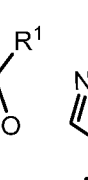
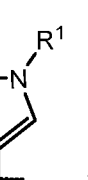
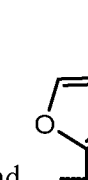
p is 0, 1, or 2.

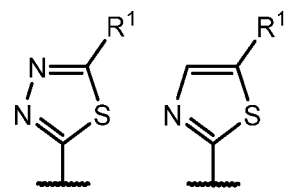
44. The method of claim 43, wherein the A ring is selected from: thiophene, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, tetrazole, and furan, each of which is optionally substituted with one or more substituents independently selected from R^1 .

45. The method of claim 44, wherein the A ring is selected from thiophene, oxadiazole, oxazole, thiadiazole, triazole, pyrazole, and thiazole, each of which is optionally substituted with one or more substituents independently selected from R^1 .

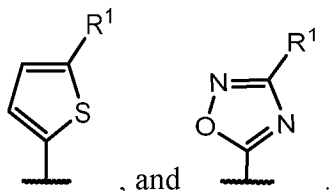
46. The method of claim 45, wherein the A ring is selected from: , , , , , , , , , and , each of which is optionally substituted with one or more substituents independently selected from R^1 .

47. The method of claim 46, wherein the A ring is selected from: , , and , each of which is optionally substituted with one or more substituents independently selected from R^1 .

48. The method of claim 46, wherein the A ring is selected from: , , , , , , , , , and .



49. The method of claim 48, wherein the A ring is selected from:



50. The method of any one of claims 43 to 49, wherein R^1 is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-CN$, 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^5 ; 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, $-OR^6$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 .

51. The method of claim 50, wherein R^1 is selected from:

C_{1-6} alkyl; 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, $-OR^6$, - and C_{1-6} alkyl, optionally substituted with one or more R^5 .

52. The method of claim 51, wherein R^1 is selected from methyl optionally substituted with one or more substituents independently selected from halogen, $-OH$, or $-OCH_3$.

53. The method of any one of claims 43 to 51, wherein R^1 is selected from pyridine, C_{3-5} cycloalkyl, and phenyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CH_3$, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-CF_3$, $-CHF_2$, $-OCHF_2$, and cyclopropyl.

54. The method of any one of claims 43 to 47 wherein ring A is unsubstituted.

55. The method of any one of claims 43 to 54, wherein R^2 is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-CN$, C_{3-10} carbocycle and 3- to 10-

membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵;

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and
-C(O)NR⁷R⁸.

56. The method of claim 55, wherein R² is selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

57. The method of claim 56, wherein R² is selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, and -CN.

58. The method of claim 55, wherein R² is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

59. The method of claim 58, wherein R² is selected from phenyl, pyridyl, pyrimidyl, thiazole, oxadiazole, and oxazole, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, CN, and C₁₋₆ alkyl.

60. The method of claim 56, wherein R² is -C(O)NR⁷R⁸.

61. The method of claim 60, wherein R⁸ is selected from:

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, wherein the C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵; and

C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, -OR⁶, -SR⁶, -N(R⁶)₂, -CN, C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R⁵.

62. The method of claim 61, wherein R^8 is selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^6$, $-CN$, 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^5 .

63. The method of claim 62 wherein R^8 is selected from methyl, ethyl, propyl, and butyl, each of which is optionally substituted with one or more halogen, $-OH$, $-CN$, $-OCH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, phenyl, or pyridyl, wherein the phenyl or pyridyl is optionally substituted with halogen, $-CH_3$, $-OH$, $-OCH_3$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

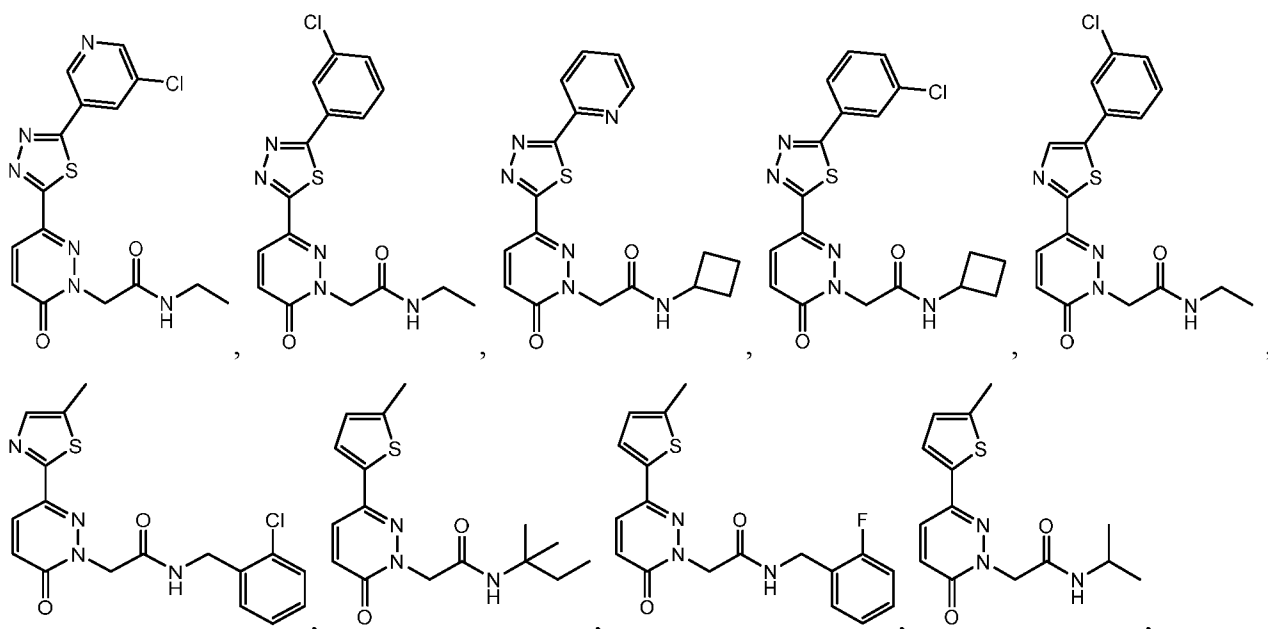
64. The method of claim 61, wherein R^8 is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^6$, $-CN$, C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are each optionally substituted with one or more R^5 .

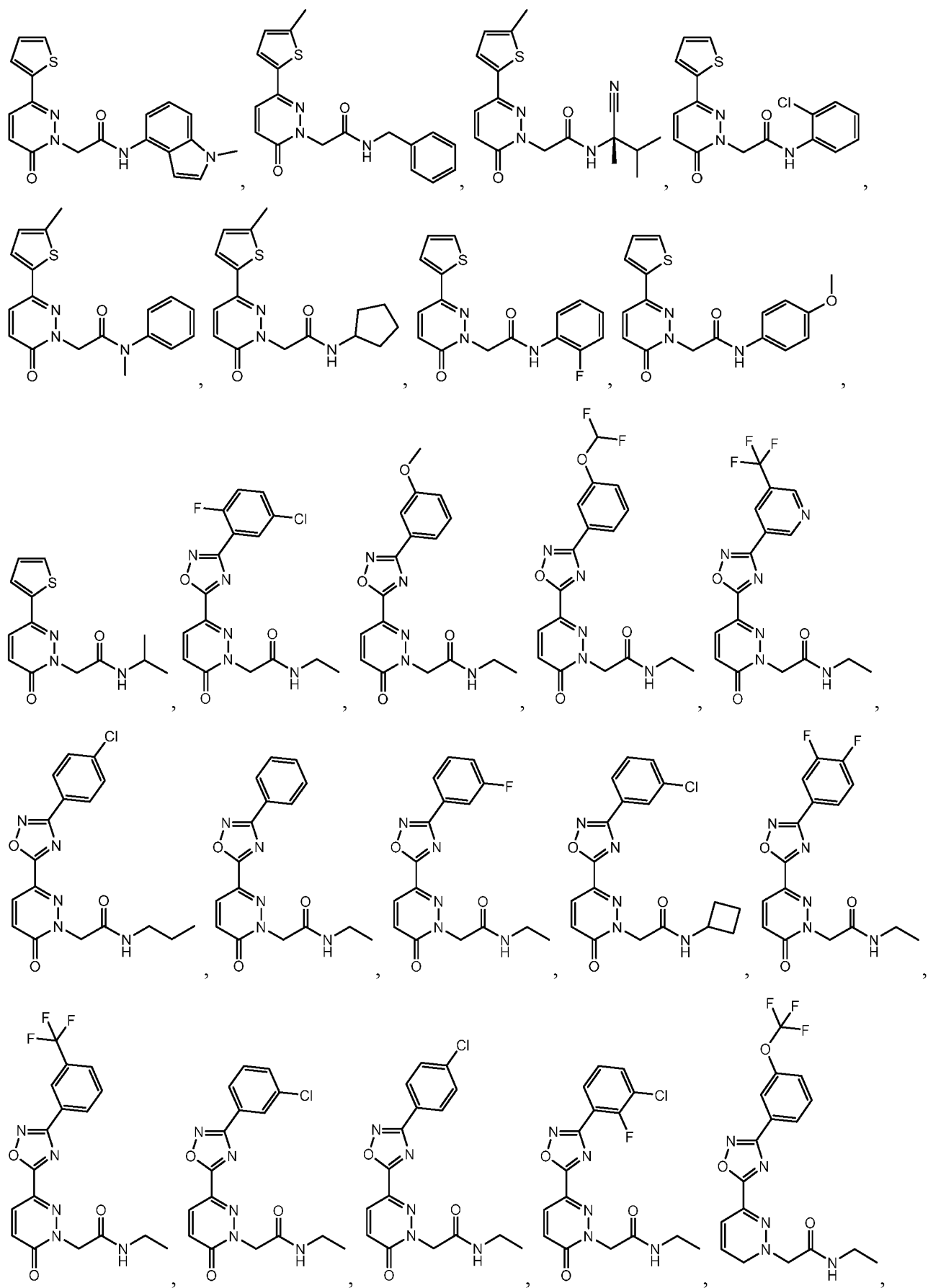
65. The method of claim 64, wherein R^8 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, oxazole, pyrazole, imidazole, triazole, pyrrole, and furan, each of which is optionally substituted with one or more R^5 .

66. The method claim 65, wherein R^8 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, and each of which is optionally substituted with one or more R^5 .

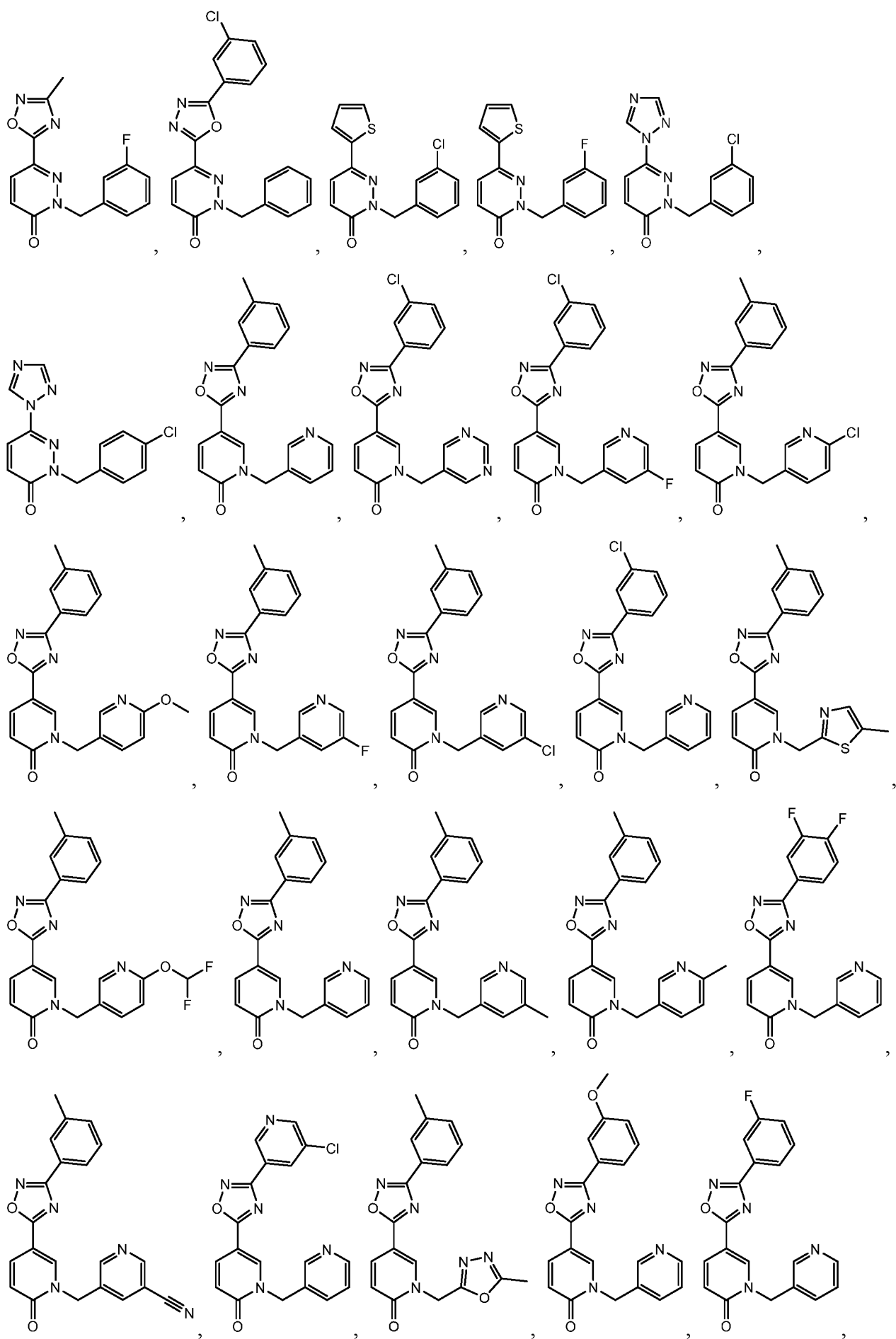
67. The method of claim 66, wherein R^8 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, oxadiazole, thiadiazole, thiazole, and each of which is optionally substituted with one or more halogen, $-CN$, $-OH$, $-OCH_3$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

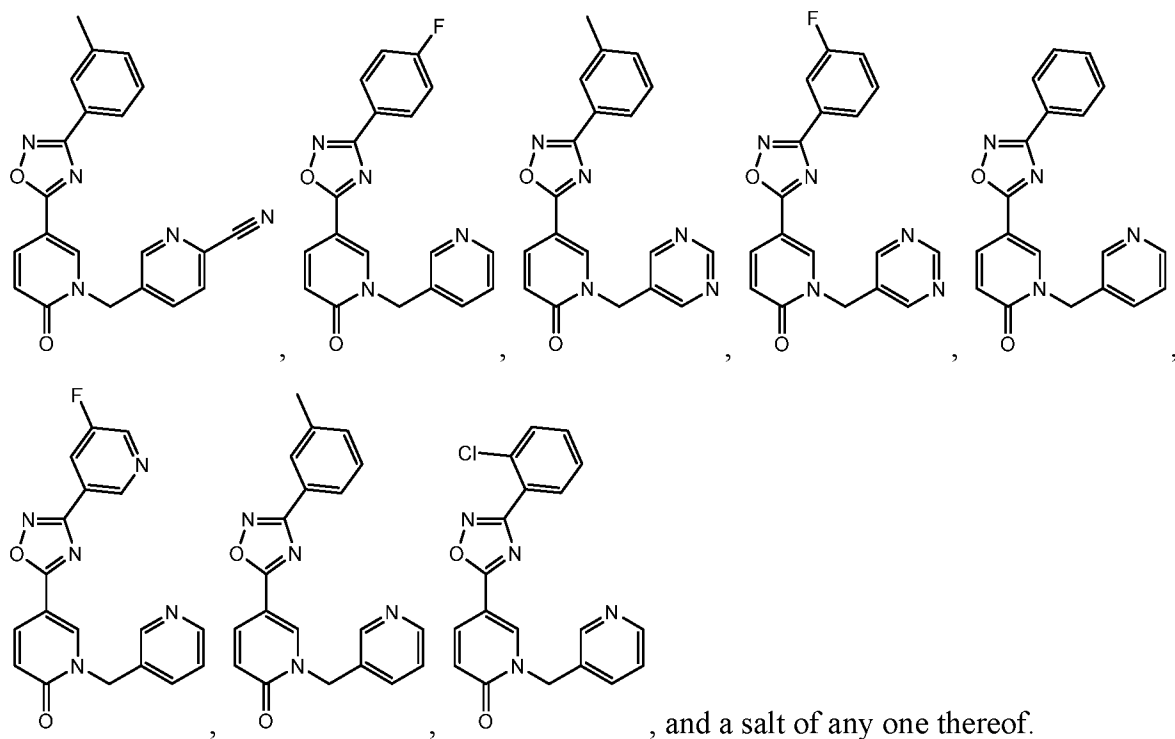
68. The method of claim 43, wherein the compound is selected from



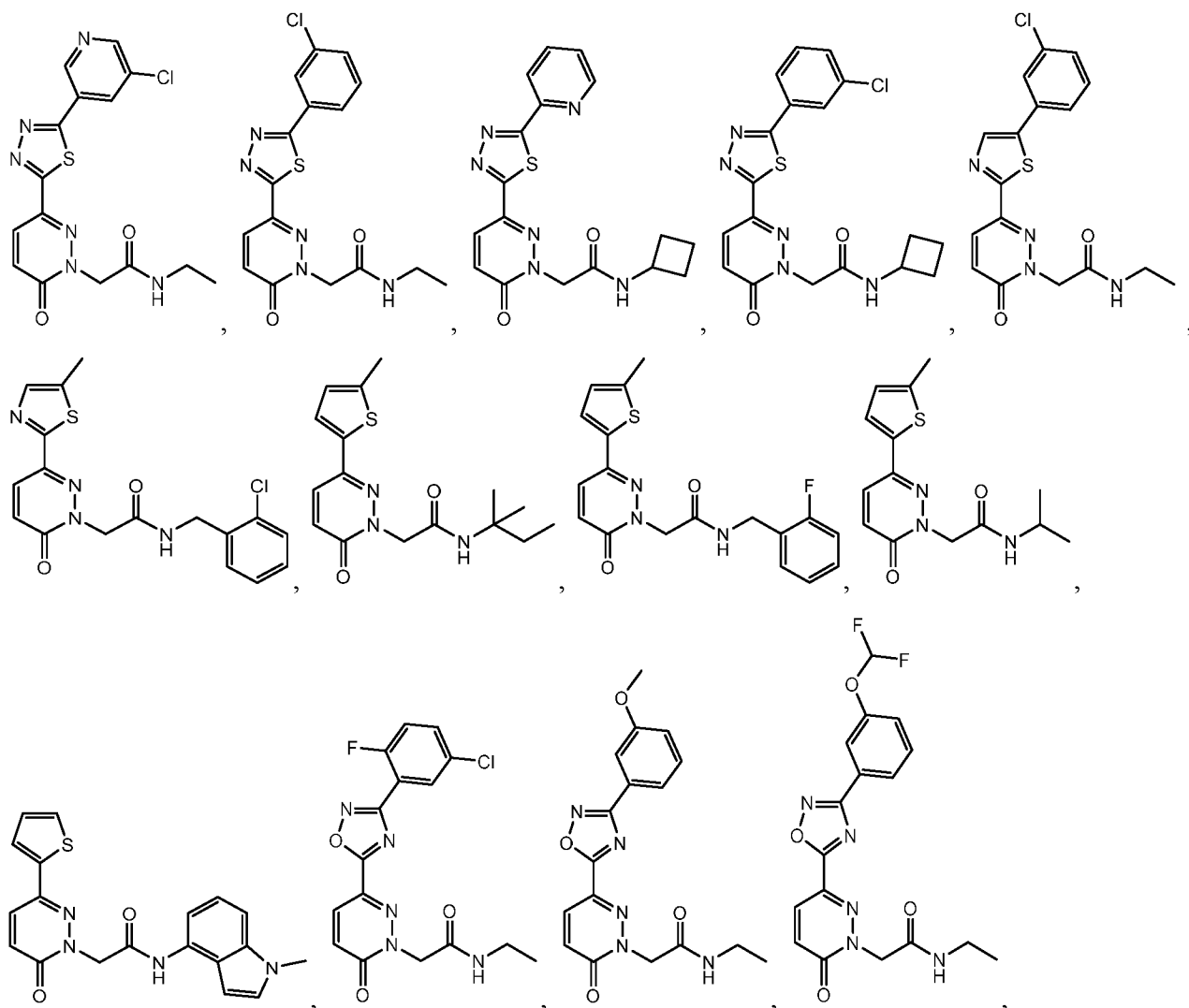




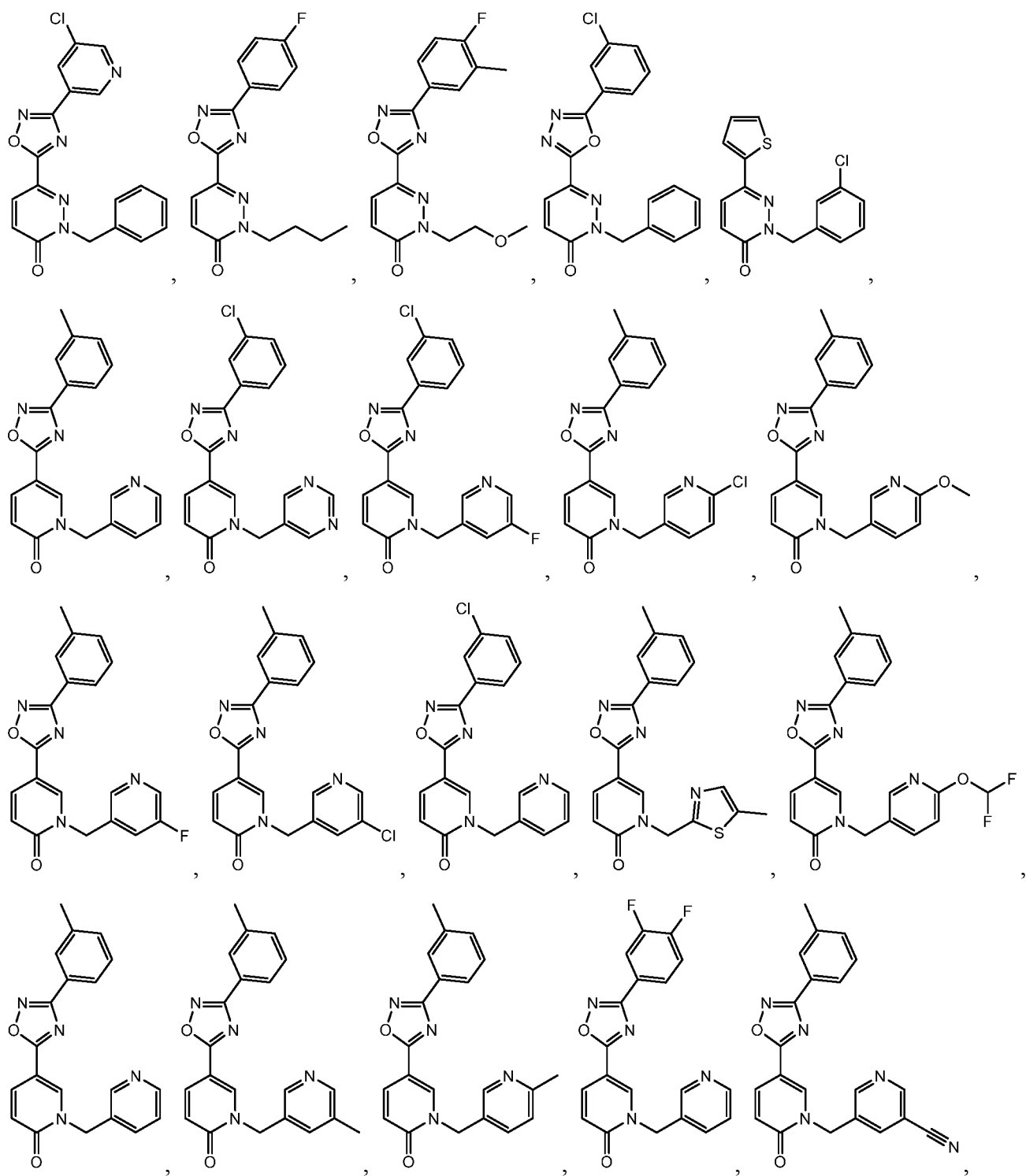


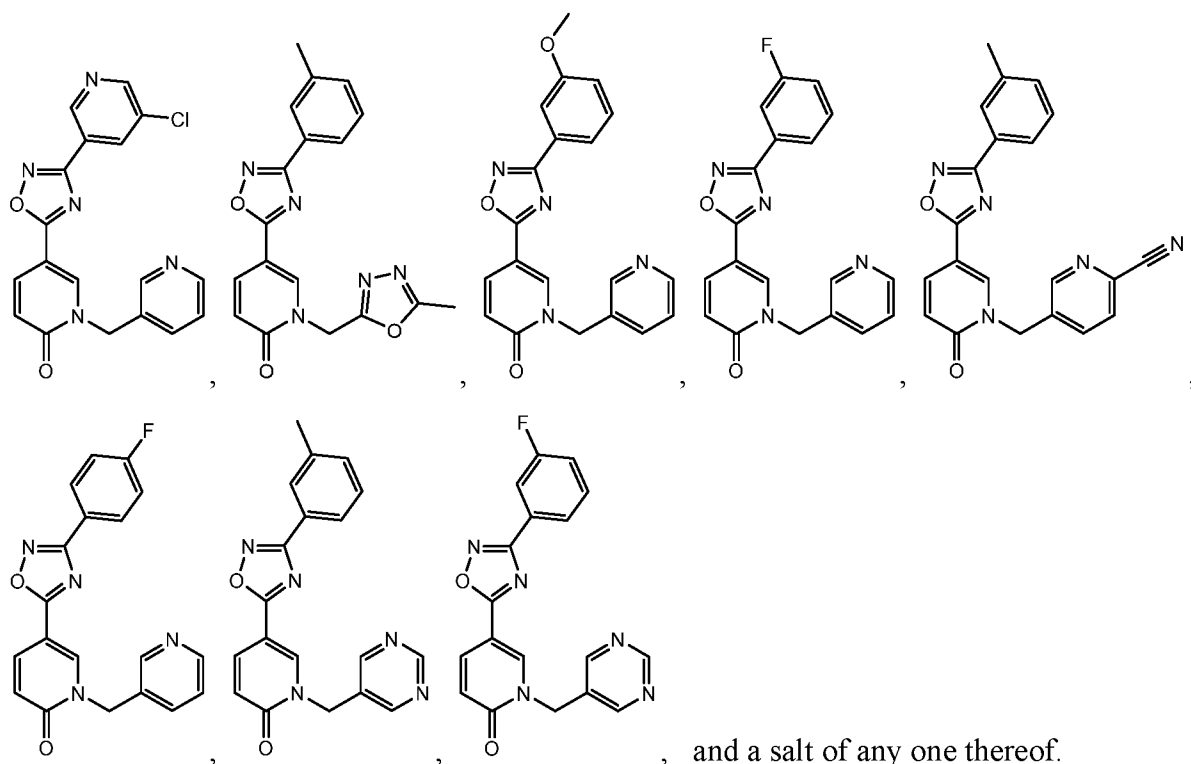


69. The method of claim 68, wherein the compound is selected from









70. The method of claim any one of claims 43 to 69, wherein the disease is a neuromuscular condition.

71. The method of claim 70, 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, carpal tunnel syndrome.

72. The method of claim 71, wherein said neuromuscular condition is Duchenne Muscular Dystrophy.

73. A method of treating a movement disorder, comprising administering to a subject in need thereof a compound or salt of any one of claims 43 to 70.

74. The method of claim 73, wherein the movement disorder comprises muscle spasticity.

75. The method of claim 74, wherein the muscle spasticity is selected from spasticity associated with multiple sclerosis, Parkinson's disease, Alzheimer's disease, or cerebral palsy, or injury, or a traumatic event such as stroke, traumatic brain injury, spinal cord injury, hypoxia, meningitis, encephalitis, phenylketonuria, or amyotrophic lateral sclerosis.

76. The method of claim 73, wherein the compound or salt is administered in an amount sufficient to reduce involuntary muscle contractions.

77. The method of claim 76, wherein the compound or salt is administered in an amount sufficient to reduce involuntary muscle contractions by at least 10%.

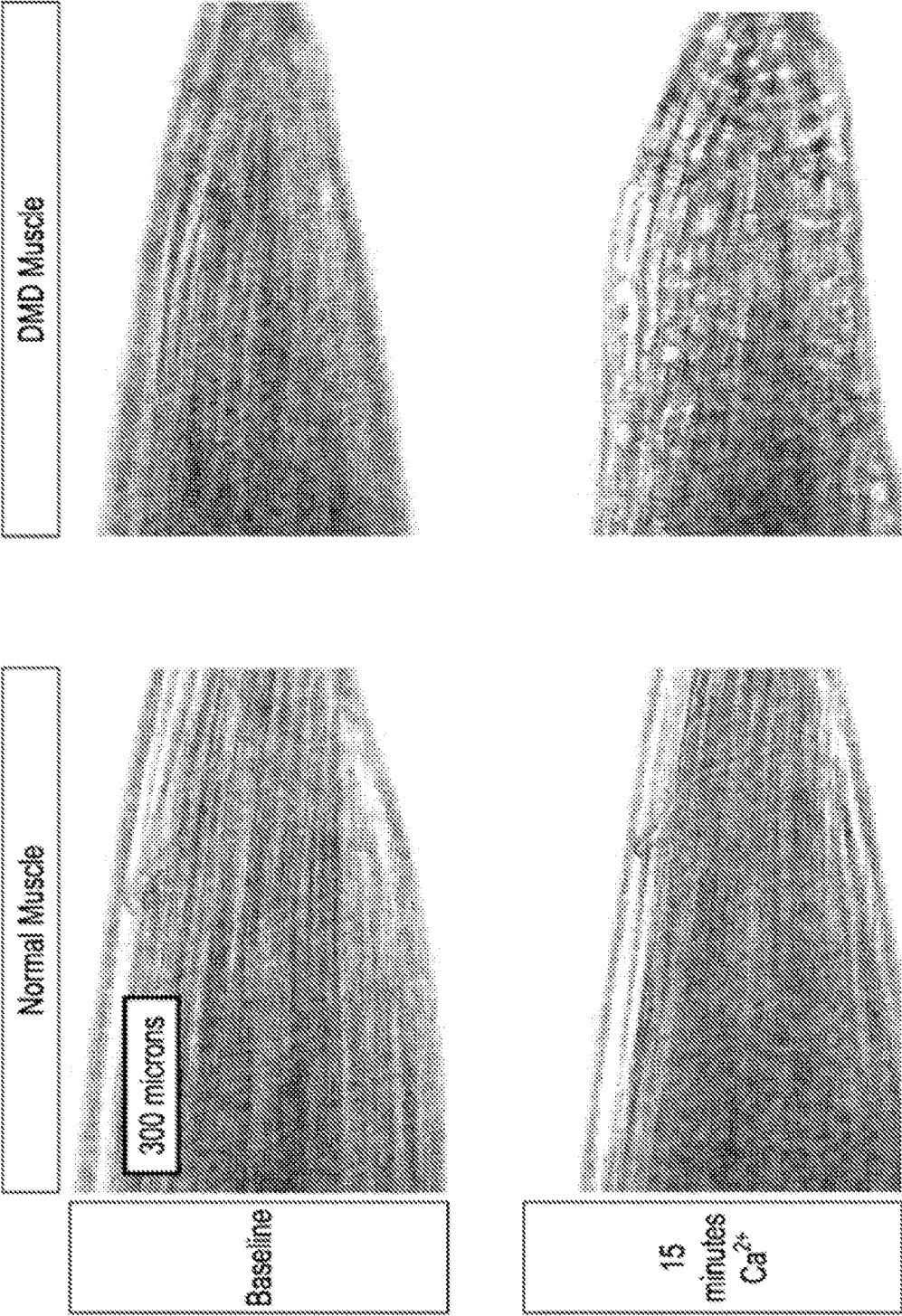


FIGURE 1

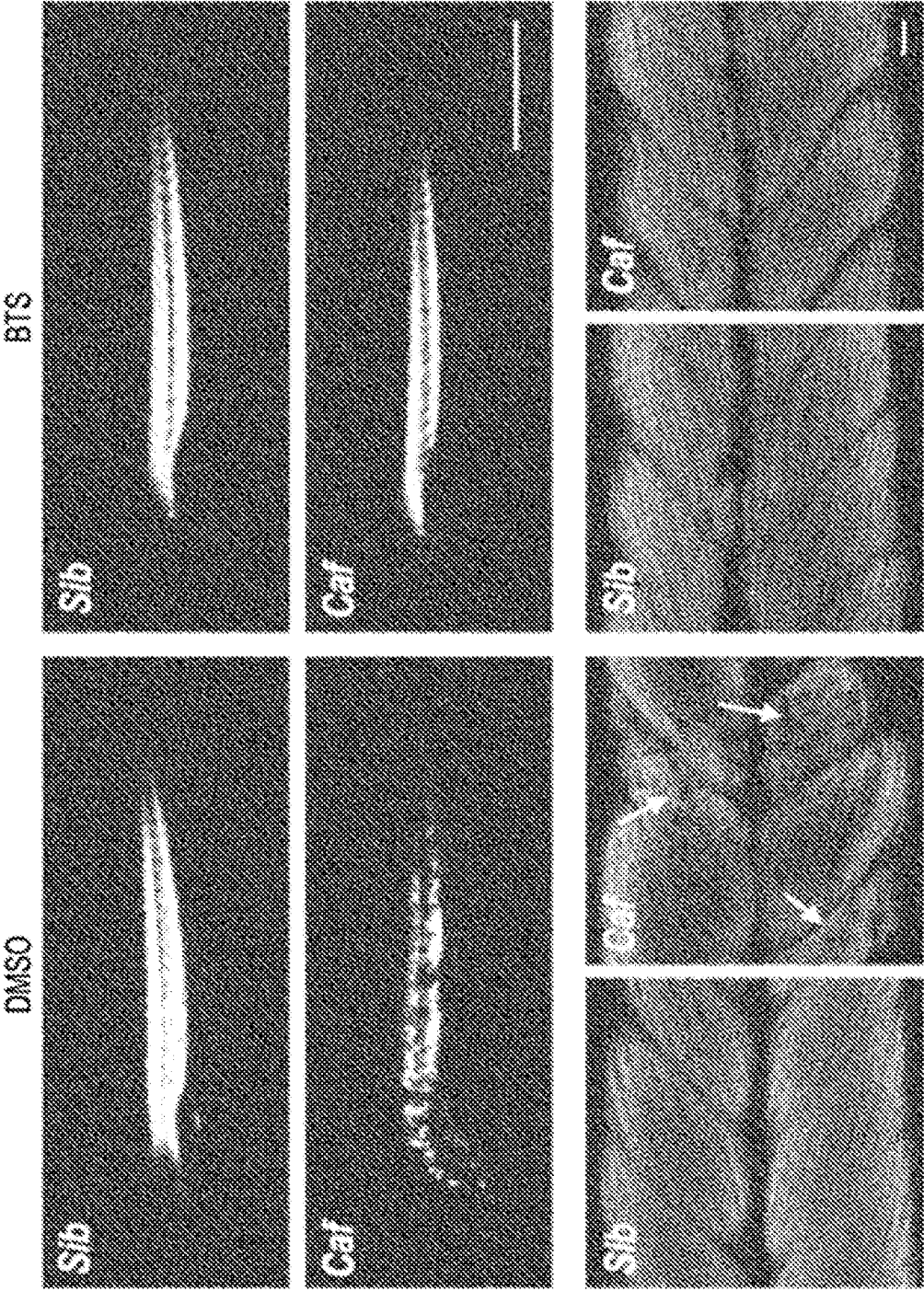


FIGURE 2

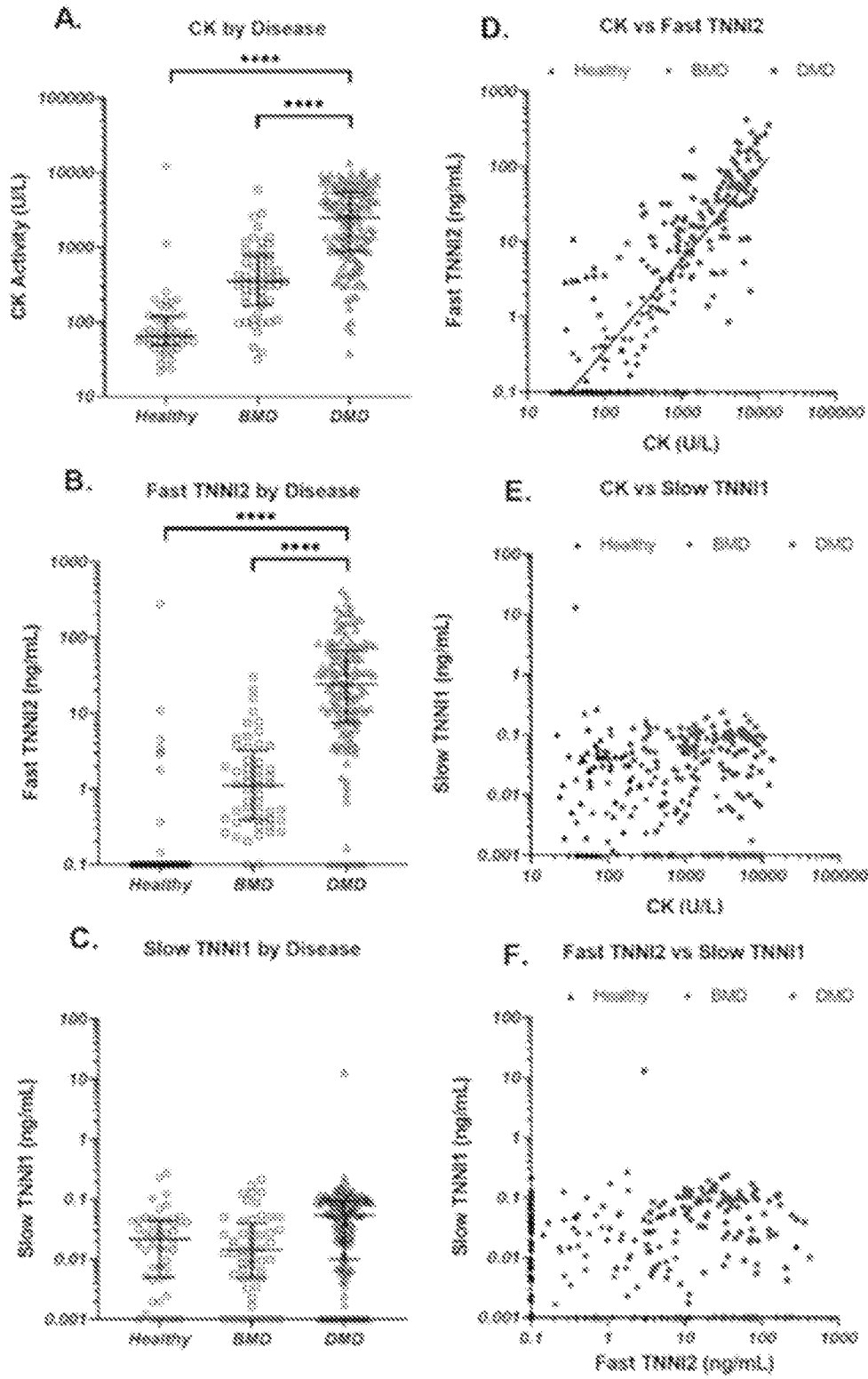


FIGURE 3

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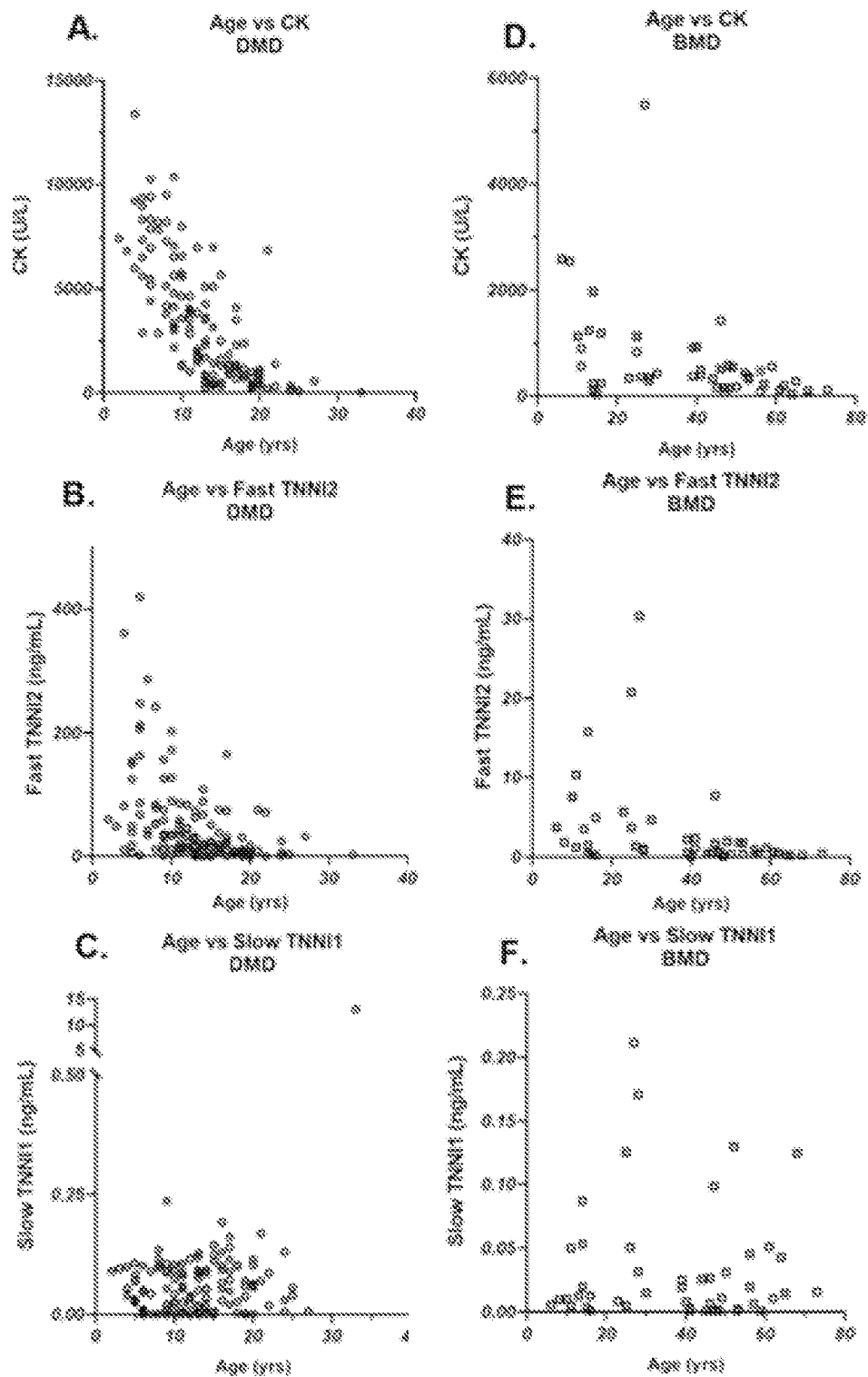


FIGURE 4

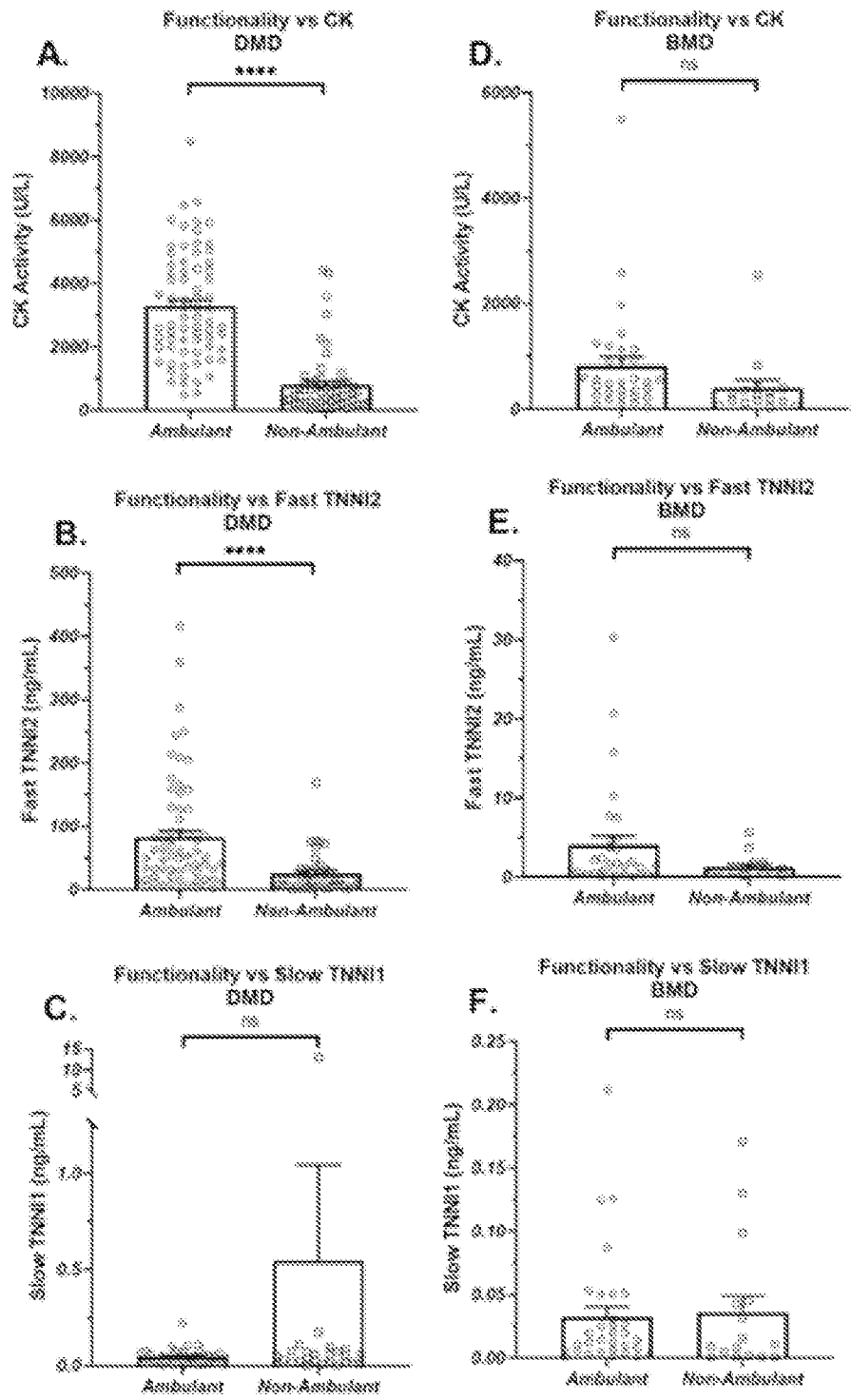


FIGURE 5

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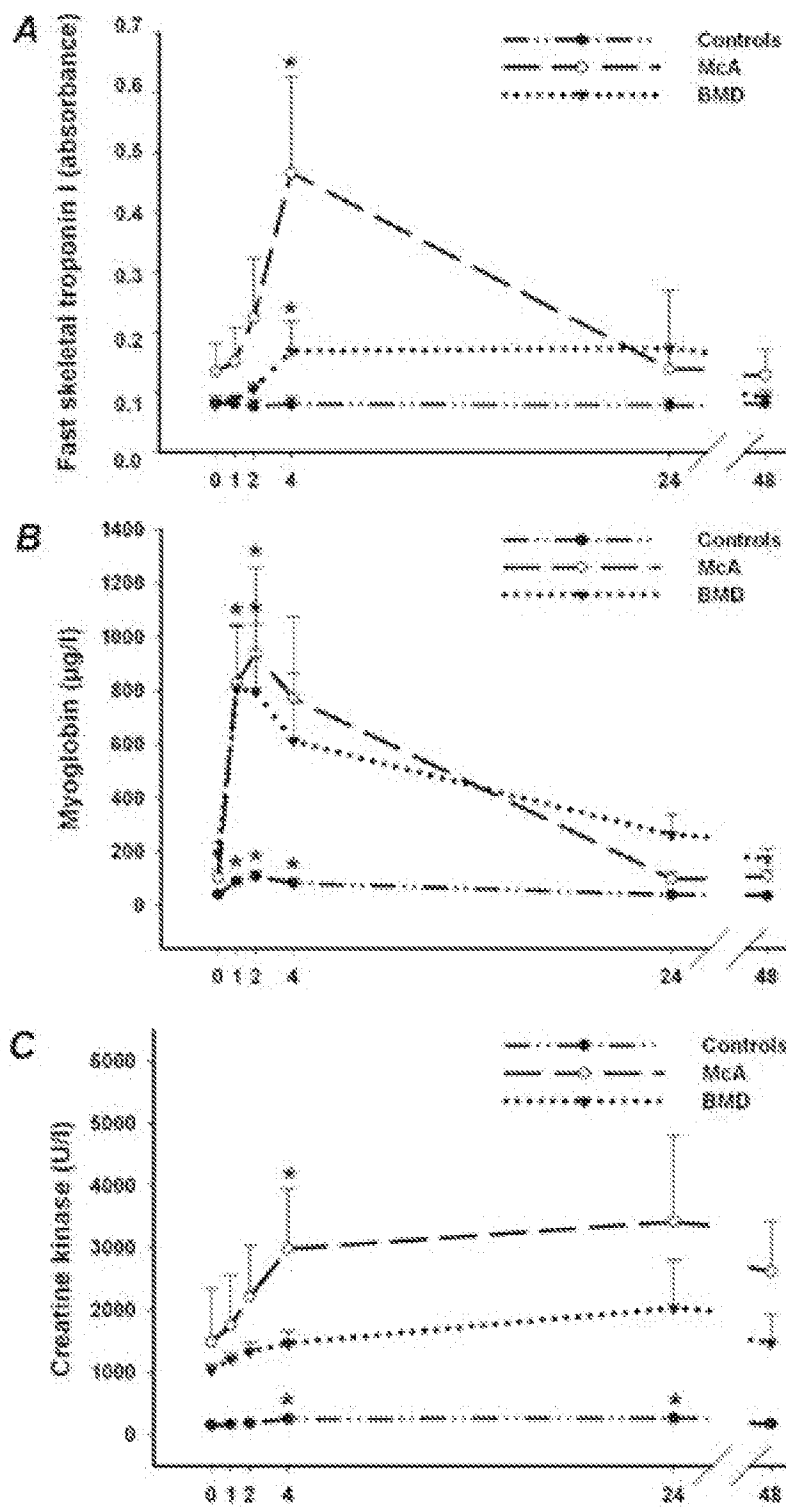


FIGURE 6

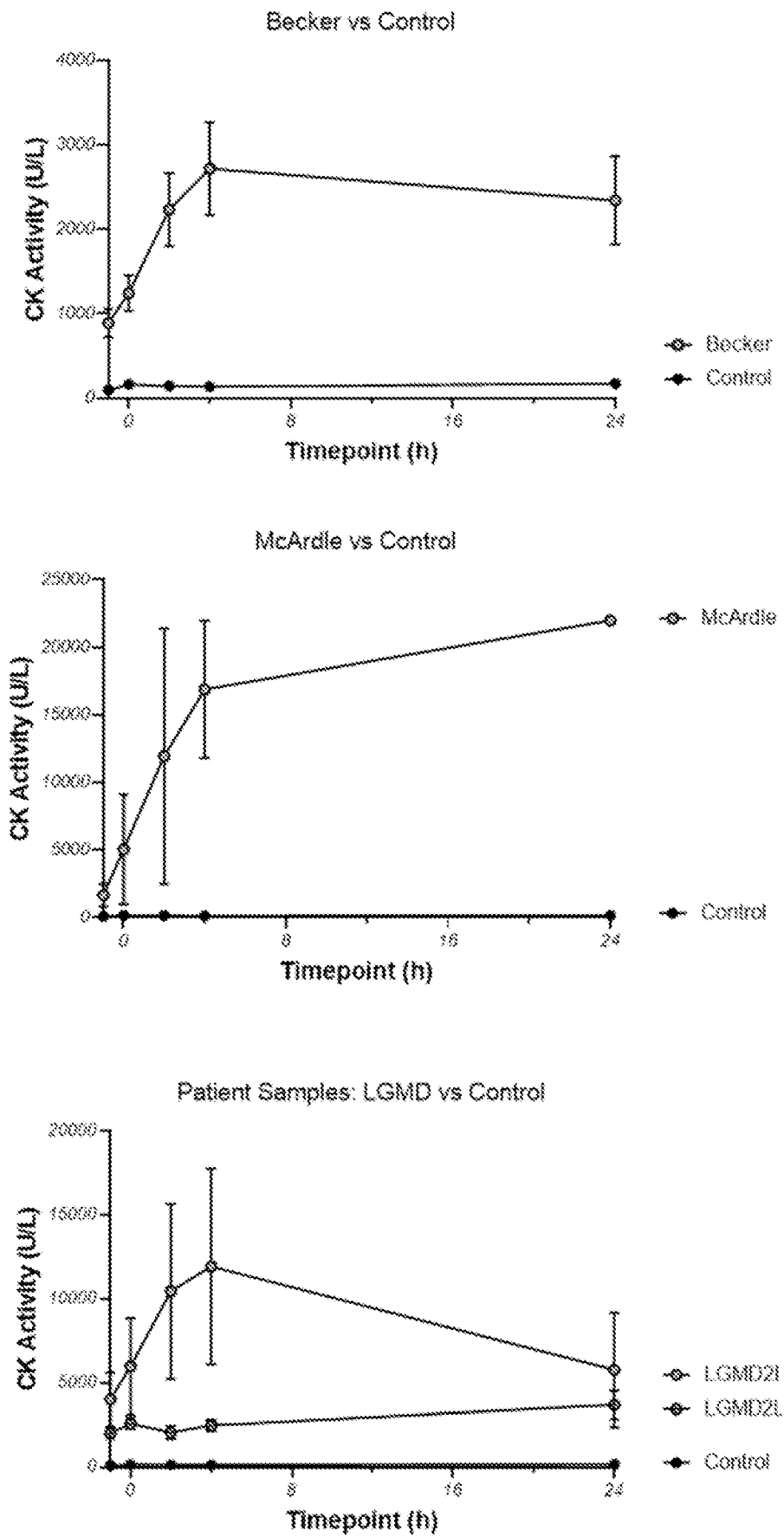


FIGURE 7

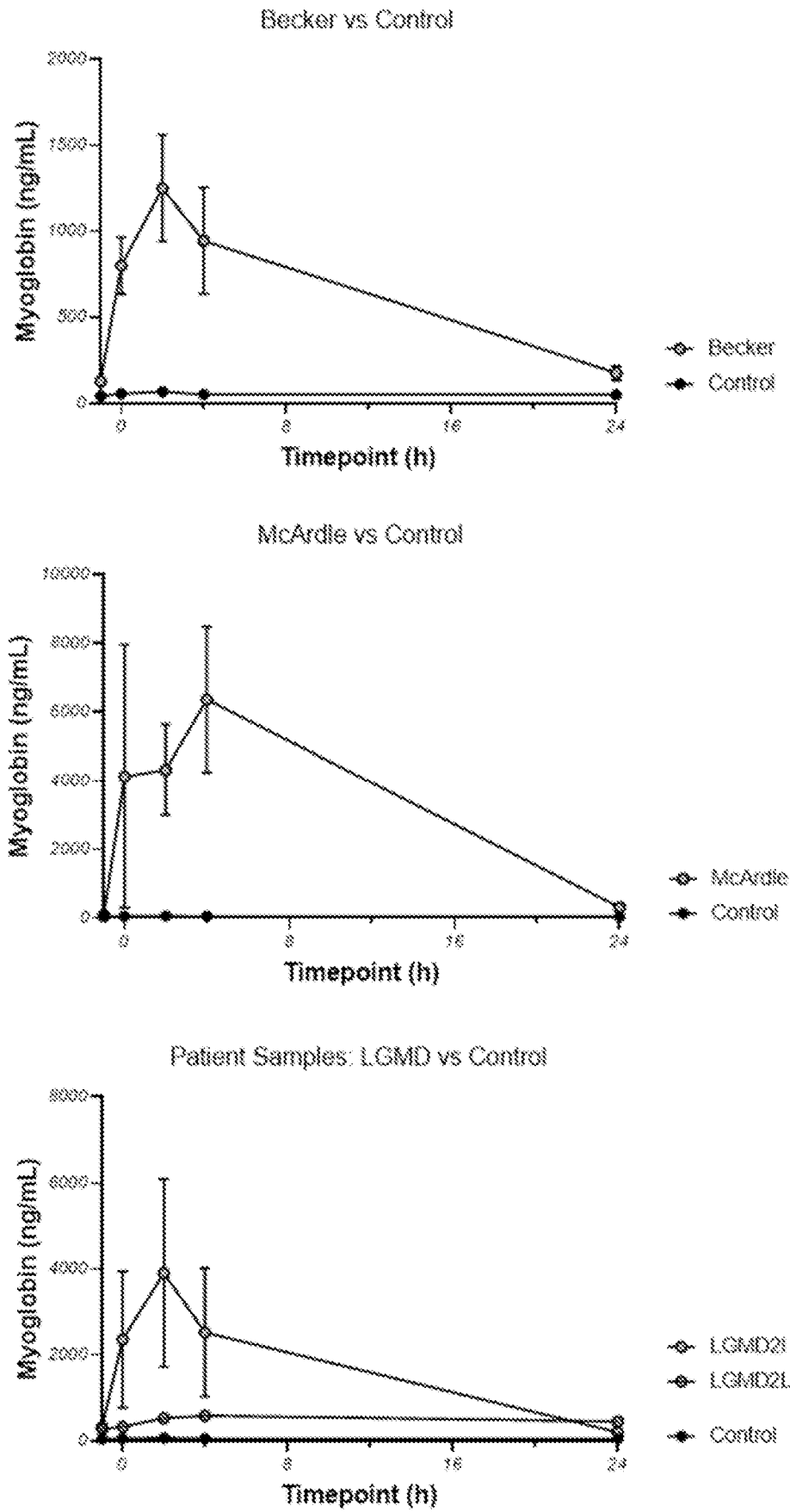


FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/031979

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P21/00 C07D409/04 C07D413/04 C07D413/14 C07D417/04
A61K31/501

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search

4 August 2021

Date of mailing of the international search report

13/08/2021

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Panday, Narendra

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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