

METHODS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

Background of the Invention

An incomplete understanding of the molecular perturbations that cause disease, as well as a limited arsenal of robust model systems, has contributed to a failure to generate successful disease-modifying therapies against common and progressive neurological disorders, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Progress is being made on many fronts to find agents that can arrest the progress of these disorders. However, the present therapies for most, if not all, of these diseases provide very little relief. Accordingly, a need exists to develop therapies that can alter the course of neurological diseases (e.g., neurodegenerative diseases). More generally, a need exists for better methods and compositions for the treatment of neurological disorders in order to improve the quality of the lives of those afflicted by such diseases.

Stearoyl-CoA desaturases (SCDs) introduce a double bond in the C9-C10 position of saturated fatty acids such as palmitoyl-CoA and stearoyl-CoA which are converted to palmitoleoyl-CoA and oleoyl-CoA, respectively. One SCD gene, SCD1, has been characterized in humans for which there are two isoforms, SCD1 and SCD5. In turn, there are two forms of SCD5, SCD5a and SCD5b, which differ at the C-terminus. The present inventors have discovered that inhibition of SCDs is capable of suppressing toxicity in cells related to protein misfolding and/or aggregation. Accordingly, inhibition of SCDs may provide new methods for the treatment of diseases and disorders related to toxicity caused by protein misfolding and/or aggregation.

Summary

This disclosure provides compounds that modulate the activity of SCDs (e.g., SCD1 and/or SCD5), pharmaceutical compositions including such compounds, and methods of utilizing such compounds and compositions for modulating the activity of SCDs for the treatment of diseases and disorders related to toxicity caused by proteins such as toxicity related to misfolding and/or aggregation of proteins. In some examples, the disease or disorder is a neurological disorders.

In one aspect, the disclosure provides use of an SCD5 inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is Parkinson's disease or dementia with Lewy bodies.

In one example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes administering an effective amount of an SCD inhibitor.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. The method includes administering an SCD inhibitor in an amount sufficient to suppress toxicity in a cell (e.g., in a mammalian neural cell) related to a protein (e.g., toxicity related to misfolding and/or aggregation of a protein such as α -synuclein or ApoE4). In some embodiments, the toxicity is α -synuclein-related toxicity. In some embodiments, the toxicity is ApoE4-related toxicity.

In another example, the disclosure provides a method of suppressing toxicity in a cell (e.g., a neural cell) related to a protein (e.g., toxicity related to misfolding and/or aggregation of a protein such as α -synuclein or ApoE4). This method includes contacting a cell with an SCD inhibitor.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes (a) determining the level (e.g., in a neural cell) of a protein or a particular form of a protein (e.g., a misfolded form of a protein) related to a neurological disorder (e.g., α -synuclein, ApoE4, or an undesired form thereof) in the subject; and (b) administering an effective

amount of an SCD inhibitor to the subject if the level of the protein or the particular form of the protein (e.g., a misfolded form of the protein) related to a neurological disorder is greater than a predetermined level (e.g., the level in a sample from a subject that does not have a neurological disorder).

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof, wherein the subject has an elevated level, or is predicted to have an elevated level (e.g., based on genetic markers) of a protein or a particular form of a protein related to a neurological disorder (e.g., α -synuclein, ApoE4, or an undesired form thereof). This method includes administering an effective amount of an SCD inhibitor to the subject. In some embodiments, the subject has an elevated level of the protein or the particular form of the protein (e.g., a misfolded form of the protein) related to a neurological disorder compared to a predetermined reference value (e.g., a value in a sample from a healthy subject).

In another example, the disclosure provides a method of treating a neurological disorder in a subject, wherein the subject has an elevated level (e.g., the subject has a level about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more greater as compared to a reference such as the level in a sample from a healthy subject) of a protein or a particular form of a protein (e.g., a misfolded form of a protein) related to a neurological disorder (e.g., α -synuclein, ApoE4, or an undesired form thereof), the method including administering an effective amount of an SCD inhibitor.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes (a) administering an effective amount of an SCD inhibitor to the subject; and (b) determining the level (e.g., in a neural cell) of a protein or a particular form of a protein related to a neurological disorder (e.g., α -synuclein, ApoE4, or an undesired form thereof) in the subject.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes (a) administering an effective amount of an SCD inhibitor to the subject; and (b) determining the level of neurite degeneration (e.g., by determining the level of a marker of neurite degeneration) in the subject.

In another example, the disclosure provides a method of suppressing neurite degeneration in a subject. This method includes administering an SCD inhibitor to the subject in an amount sufficient to suppress neurite degeneration.

In some embodiments of any of the foregoing methods, the SCD inhibitor is an SCD1 inhibitor. In some embodiments of any of the foregoing methods, the SCD inhibitor is an SCD5 inhibitor. In some embodiments, the SCD inhibitor is selective for SCD1 over SCD5. In some embodiments of any of the foregoing methods, the SCD inhibitor has activity for SCD1 that is at least 2.5-fold greater (e.g., at least 5-fold greater, at least 10-fold greater, at least 20-fold greater) than the activity of the inhibitor for SCD5. In some embodiments, the SCD inhibitor is selective for SCD5 over SCD1. In some embodiments of any of the foregoing methods, the SCD inhibitor has activity for SCD5 that is at least 2.5-fold greater (e.g., at least 5-fold greater, at least 10-fold greater, at least 20-fold greater) than the activity of the inhibitor for SCD1. In some embodiments, the SCD inhibitor is a non-selective SCD inhibitor.

In some embodiments of any of the foregoing methods, the SCD inhibitor is any compound described herein (e.g., any compound having the structure of any one of Formula I-LXI). In some

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In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula I. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula II. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula III. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula IV. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula V. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula VI. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula VII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula VIII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula IX. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula X. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula XI. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula XII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula XIII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula XIV. In some

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LII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LIII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LIV. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LV. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LVI. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LVII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LVIII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LIX. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LX. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of Formula LXI.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of any one of Formula I-XXX. In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of any one of Formula XXXI-XLII. In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of any one of Formula XLIII-XLIV. In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of any one of Formula XLVI-XLVII. In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of any one of Formula L-LX.

In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of any one of Formula I-XXX. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of any one of Formula XXXI-XLII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of any one of Formula XLIII-XLIV. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of any one of Formula XLVI-XLVII. In some embodiments of any of the foregoing methods, the SCD inhibitor is not a compound of any one of Formula L-LX.

In some embodiments of any of the foregoing methods, a cell expresses α -synuclein and/or a human apolipoprotein E (ApoE) protein (e.g., ApoE2, ApoE3, or ApoE4).

In some embodiments of any of the foregoing methods, the subject carries one or two copies of the ApoE4 allele).

In some embodiments of any of the foregoing methods, the subject is a human.

In some embodiments of any of the foregoing methods, the cell is a neural cell (e.g., a neuron or glial cell).

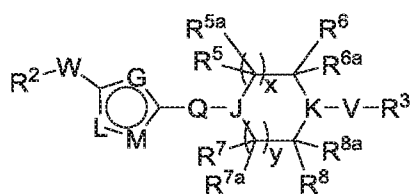
In some embodiments of any of the foregoing methods, the method includes inhibition of neurite degeneration or cell death.

Neurological disorders include, but are not limited to Alexander disease, Alpers' disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, Steele-Richardson-Olszewski disease, tabes dorsalis, frontal temporal dementia, vascular dementia, Down's syndrome, and Guillain-Barre Syndrome.

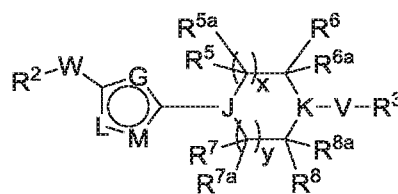
In some embodiments of any of the foregoing methods, the neurological disorder is a proteopathy (e.g., a synucleinopathy, AD, Alexander disease, amyotrophic lateral sclerosis (ALS), a prion disease (e.g., Creutzfeldt-Jakob disease), Huntington's disease, Machado-Joseph disease, Pick's disease, or frontotemporal dementia). In some embodiments of any of the foregoing methods, the neurological disorder is a synucleinopathy such as Parkinson's disease (PD), dementia with Lewy bodies, pure autonomic failure, multiple system atrophy, incidental Lewy body disease, pantothenate kinase-associated neurodegeneration, Alzheimer's disease, Down's Syndrome, Gaucher disease, or the Parkinsonism-dementia complex of Guam. In some embodiments of any of the foregoing methods, the neurological disorder is a progressive neurodegenerative disorder (e.g. Alpers' disease, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Kennedy's disease, Krabbe disease, Pelizaeus-Merzbacher disease, primary lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, Steele-Richardson-Olszewski disease, tabes dorsalis, vascular dementia, or Guillain-Barre Syndrome). In some embodiments of any of the foregoing methods, the neurological disorder is an ApoE-associated neurodegenerative disorder (e.g., AD, vascular cognitive impairment, cerebral amyloid angiopathy, traumatic brain injury, or multiple sclerosis).

In some embodiments of any of the foregoing methods, the method further includes administering an additional therapeutic agent (e.g., a small molecule, an antibody or fragment thereof, or a nucleic acid) to the subject. In some embodiments of any of the foregoing methods, the method further includes administering to the subject a cognition-enhancing agent, an antidepressant agent, an anxiolytic agent, an antipsychotic agent, a sedative, a dopamine promoter, or an anti-tremor agent. In some embodiments, the additional therapeutic agent and the SCD inhibitor are administered within 28 days of each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) in amounts that together are effective to treat the subject.

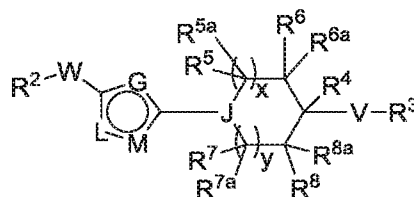
In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula Ia-Ic:



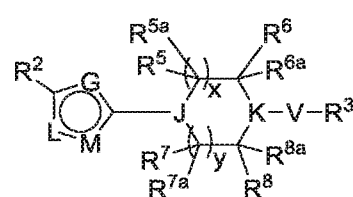
(Ia)



(Ib)



(Ic)



(Id)

wherein:

x and y are each independently 0, 1, 2 or 3;

each R¹ is independently selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂hydroxyalkyl, C₄-C₁₂cycloalkylalkyl and C₇-C₁₉aralkyl;

each R⁴ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, haloalkyl, cyano, nitro or -N(R⁹)₂;

or two adjacent R⁴ groups, together with the carbons to which they are attached, may form an aryl, heteroaryl or heterocyclyl ring system;

R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

or R⁵ and R^{5a} together, R⁶ and R^{6a} together, or R⁷ and R^{7a} together, or R⁸ and R^{8a} together are an oxo group, provided that when V is -C(O)-, R⁶ and R^{6a} together or R⁸ and R^{8a} together do not form an oxo group, while the remaining R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

or one of R⁵, R^{5a}, R⁶ and R^{6a} together with one of R⁷, R^{7a}, R⁸ and R^{8a} forms a direct bond or an alkylene bridge, while the remaining R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl; and

each R⁹ is independently selected from hydrogen or C₁-C₆alkyl.

In some embodiments of the compound of Formula Ia,

G is -N(R⁴)-, -O-, -S(O)_t- (where t is 0, 1 or 2), -C(R⁴)= or -C(R⁴)=C(R⁴)-;

J and K are each independently N or C(R¹⁰);

L and M are each independently -N= or -C(R⁴)=, provided that when G is -C(R⁴)= or -C(R⁴)=C(R⁴)-, L and M cannot both be -C(R⁴)=;

Q is -N(R⁴)-, -O-, -S(O)_t- (where t is 0, 1 or 2), -C(O)-, -C(S)-, an alkylene chain or an alkenylene chain;

V is a direct bond, -N(R¹)-, -N(R¹)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_t- (where t is 0, 1 or 2) or -S(O)_pN(R¹)- (where p is 1 or 2);

W is a direct bond, -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_p- (where p is 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(O)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O- or -C(R¹)₂-;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy; or as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

In some embodiments of the compound of Formula Ib,

G is -N(R⁴)-, -O-, or -S(O)_t- (where t is 0, 1 or 2);

J and K are each independently N or C(R¹¹);

L and M are each independently -N= or -C(R⁴)=;

V is -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(R¹⁰)H-, -N(R¹)-, -O-;

W is a direct bond, -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_p- (where p is 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(O)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-;

R² is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl; or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl; or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R¹⁰ is a hydrogen or C₁-C₃alkyl; and

R¹¹ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy; or a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments of the compound of Formula Ic,

G is -N(R⁴)-, -O-, -S(O)_t- (where t is 0, 1 or 2), -C(R⁴)= or -C(R⁴)=C(R⁴)-;

J is N or C(R¹⁰);

L and M are each independently -N= or -C(R⁴)=, provided that when G is -C(R⁴)= or -C(R⁴)=C(R⁴)-, L and M cannot both be -C(R⁴)=;

V is a direct bond, -N(R¹)-, -N(R¹)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_p- (where p is 1 or 2), or -S(O)_pN(R¹)- (where p is 1 or 2);

W is -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_p- (where p is 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(O)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O- or -C(R¹)₂-;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

5 R³ is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

10 R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy; or as a stereoisomer, enantiomer or tautomer thereof, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

In some embodiments of the compound of Formula Id,

G is -N(R⁴)-, -O-, -S(O)_t (where t is 0, 1 or 2), -C(R⁴)= or -C(R⁴)=C(R⁴)-;

15 J and K are each independently N or C(R¹⁰);

L and M are each independently -N= or -C(R⁴)=, provided that when G is -C(R⁴)= or -C(R⁴)=C(R⁴)-, L and M cannot both be -C(R⁴)=;

V is direct bond, -N(R¹)-, -N(R¹)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_p- (where p is 1 or 2), or -S(O)_pN(R¹)- (where p is 1 or 2);

20 R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

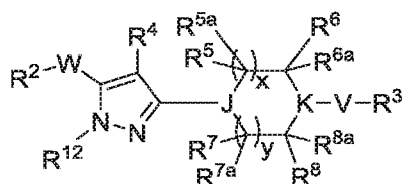
or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

25 R³ is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

30 R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy; or as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

35 In some embodiments, the disclosure provides compounds of Formula Ib having the following Formula Iba:



(Iba)

wherein:

x and y are each independently 1, 2 or 3;

M is $-\text{C}(\text{R}^4)=$ or $-\text{N}=$;

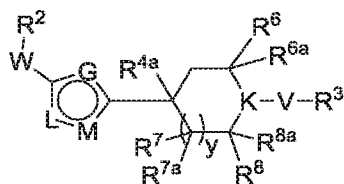
5 R^{12} is hydrogen, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, C_1 - C_{12} alkyl, C_2 - C_{12} hydroxyalkyl, C_4 - C_{12} cycloalkylalkyl or C_7 - C_{19} aralkyl; and

each R^{13} is independently selected from hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl; or

10 as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

Compounds of Formula (I) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2006/034341, WO2006/034315, WO2006/034338, and WO2006/034440. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2006/034341, WO2006/034315, WO2006/034338, and WO2006/034440, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula II:



(II)

wherein:

y is 0, 1, 2, or 3;

G is $-\text{N}(\text{R}^4)-$, $-\text{O}-$, $-\text{S}(\text{O})_t-$ (where t is 0, 1 or 2), $-\text{C}(\text{R}^4)=$ or $-\text{C}(\text{R}^4)=\text{C}(\text{R}^4)-$;

K is N or $\text{C}(\text{R}^{10})$;

L and M are each independently $-\text{N}=$ or $-\text{C}(\text{R}^4)=$, provided that when G is $-\text{C}(\text{R}^4)=$ or $-\text{C}(\text{R}^4)=\text{C}(\text{R}^4)-$, L and M cannot both be $-\text{C}(\text{R}^4)=$;

V is $-\text{N}(\text{R}^1)-$, $-\text{O}-$, $-\text{C}(\text{R}^{10})_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{R}^1)-$, $-\text{S}(\text{O})_t-$ (where t is 0, 1 or 2) or $-\text{S}(\text{O})_p\text{N}(\text{R}^1)-$ (wherein p is 1 or 2), provided that when K is N, V cannot be $-\text{S}-$;

W is a direct bond, $-\text{N}(\text{R}^1)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^1)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^1)-$, $-\text{N}(\text{R}^1)\text{C}(\text{O})\text{N}(\text{R}^1)-$, $-\text{O}-$, $-\text{N}(\text{R}^1)-$, $-\text{S}(\text{O})_t-$ (where t is 0, 1 or 2), $-\text{N}(\text{R}^1)\text{S}(\text{O})_p-$ (where p is 1 or 2), $-\text{S}(\text{O})_p\text{N}(\text{R}^1)-$ (where p is 1 or 2), $-\text{C}(\text{O})-$, $-\text{OS}(\text{O})_2\text{N}(\text{R}^1)-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{N}(\text{R}^1)\text{C}(\text{O})\text{O}-$;

each R^1 is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl,

C₂-C₁₂hydroxyalkyl, C₄-C₁₂cycloalkylalkyl and C₇-C₁₉aralkyl;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

5 or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, 10 C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R⁴ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, 15 haloalkyl, cyano, nitro or -N(R⁹)₂;

or two adjacent R⁴ groups, together with the carbons to which they are attached, may form an aryl, heteroaryl or heterocyclyl ring system;

R^{4a} is hydrogen, fluoro, chloro, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, haloalkyl, cyano, nitro or -N(R⁹)₂;

or R^{4a} is a direct bond to an adjacent carbon;

20 R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

or R⁶ and R^{6a} together, or R⁷ and R^{7a} together, or R⁸ and R^{8a} together are an oxo group, provided that when V is -C(O)-, R⁶ and R^{6a} together or R⁸ and R^{8a} together do not form an oxo group, while the remaining R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

or one of R⁶ and R^{6a} together with one of R⁷, R^{7a}, R⁸ and R^{8a} forms a direct bond or an alkylene 25 bridge, while the remaining R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

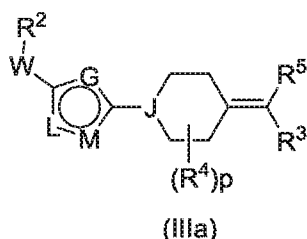
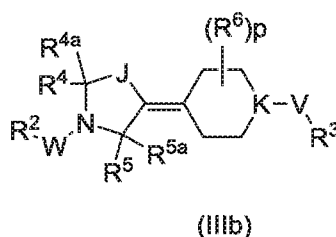
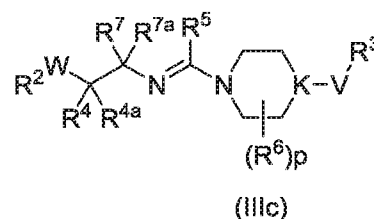
each R⁹ is independently selected from hydrogen or C₁-C₈alkyl; and

R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy; or

30 as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

Compounds of Formula (II) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2006/034279. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2006/034279, the compounds of which are herein incorporated by reference.

35 In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula III:



wherein:

p is 0 to 8;

each R¹ is independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl,

5 cycloalkylalkyl and aralkyl;

each R^{1a} is selected from the group consisting of hydrogen, C₁-C₆alkyl, cycloalkylalkyl, -OR¹, and cyano;

R² is selected from the group consisting of alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

or a stereoisomer, enantiomer or tautomer thereof, or a racemic or non-racemic mixture thereof, or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments of the compound of Formula IIIa,

W is -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -C(O)-, -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-, -N(R¹)C(NR^{1a})N(R¹)-, -N(R¹)C(S)N(R¹)-, -N(R¹)C(NR^{1a})-, -C(NR^{1a})N(R¹)-, heteroaryl, heterocyclyl or a direct bond;

L and M are independently selected from -N= or -C(R⁴)=;

G is selected from $-C(R^4)=C(R^4)-$, $-C(R^4)=N-$, $-N=C(R^4)-$, $-N=N-$, $-N(R^4)-$, $-O-$ or $-S(O)_t-$ (where t is 0, 1 or 2);

J is selected from N or C(R⁶);

each R⁴ is alkyl;

or one of R⁴ together with another one of R⁴ on a different carbon atom forms an alkylene bridge, while the remaining R⁴'s are each alkyl;

R⁵ is independently selected from hydrogen, alkyl, fluoro, chloro, or -C(O)OR⁷;

R⁶ is selected from hydrogen, alkyl, fluoro, or chloro; and

R⁷ is hydrogen, alkyl, aryl or aralkyl.

In some embodiments of the compound of Formula IIIb,

W is $-N(R^1)C(O)-R^9$ -, $-S(O)_t-R^9$ - (where t is 1, 2), $-C(O)-R^9$ -, $-OC(O)-R^9$ -, $-N(R^1)C(NR^{1a})-R^9$ -, $-C(NR^{1a})-R^9$ -, $-N(R^1)C(S)-R^9$ -, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl or a direct bond;

K is selected from N or $C(R^7)$;

5 when K is N, V is $-C(O)-$ -, $-C(O)O-$ -, $-C(S)-$ -, $-C(O)N(R^1)-$ -, $-S(O)_t$ (where t is 0, 1 or 2), $-S(O)_qN(R^1)-$ (where q is 1 or 2), $-C(R^8)H-$ or $-C(NR^{1a})-$;

when K is $C(R^7)$, V is $-O-$ -, $-C(O)-$ -, $-C(O)O-$ -, $-OC(O)-$ -, $-C(S)-$ -, $-C(O)N(R^1)-$ -, $-N(R^1)C(O)-$ -, $-S(O)_t$ - (where t is 0, 1 or 2), $-S(O)_qN(R^1)-$ (where q is 1 or 2), $-N(R^1)S(O)_q-$ (where q is 1 or 2), $-C(R^8)H-$ or $-C(NR^{1a})-$;

10 J is selected from $-O-$ -, $-N(R^1)-$ -, $-S(O)_t$ - (where t is 0, 1 or 2) or $-C(R^8)_2-$;

R^4 and R^{4a} are each independently selected from hydrogen or alkyl,

or R^4 and R^{4a} together form an oxo group;

R^5 and R^{5a} are each independently selected from a hydrogen or alkyl,

or R^5 and R^{5a} together form an oxo group;

15 each R^6 is alkyl;

or one of R^6 together with another R^6 on different carbon atom from an alkylene bridge and the other R^6 's are each alkyl;

R^7 is selected from hydrogen, alkyl, fluoro, or chloro;

R^8 is selected from hydrogen, alkyl, fluoro, chloro, methoxy, trifluoromethyl, cyano, nitro or

20 $-N(R^1)_2$; and

each R^9 is independently a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain.

In some embodiments of the compound of Formula IIIc,

25 W is $-N(R^1)C(O)-$ -, $-C(O)N(R^1)-$ -, $-OC(O)N(R^1)-$ -, $-N(R^1)C(O)N(R^1)-$ -, $-O-$ -, $-N(R^1)-$ -, $-S(O)_t$ - (where t is 0, 1 or 2), $-C(O)-$ -, $-N(R^1)S(O)_2-$ -, $-S(O)_2N(R^1)-$ -, $-OS(O)_2N(R^1)-$ -, $-OC(O)-$ -, $-C(O)O-$ -, $-N(R^1)C(O)O-$ -, $-N(R^1)C(NR^{1a})N(R^1)-$ -, $-N(R^1)C(S)N(R^1)-$ -, $-N(R^1)C(NR^{1a})-$ -, $-C(NR^{1a})N(R^1)-$ -, heteroaryl, heterocyclyl or a direct bond;

K is selected from N or $C(R^9)$;

30 when K is N, V is $-C(O)-$ -, $-C(O)O-$ -, $-C(S)-$ -, $-C(O)N(R^1)-$ -, $-S(O)_t$ (where t is 0, 1 or 2), $-S(O)_qN(R^1)-$ (where q is 1 or 2), $-C(R^8)H-$ or $-C(NR^{1a})-$;

when K is $C(R^9)$, V is $-O-$ -, $-C(O)-$ -, $-C(O)O-$ -, $-OC(O)-$ -, $-C(S)-$ -, $-C(O)N(R^1)-$ -, $-N(R^1)C(O)-$ -, $-S(O)_t$ - (where t is 0, 1 or 2), $-S(O)_qN(R^1)-$ (where q is 1 or 2), $-N(R^1)S(O)_q-$ (where q is 1 or 2), $-C(R^8)H-$ or $-C(NR^{1a})-$;

35 R^4 and R^{4a} are each independently selected from the group consisting of hydrogen, alkyl, aryl, fluoro or chloro;

or R^4 and R^{4a} together form an oxo group;

R^5 is selected from alkyl, aryl, heteroaryl, cyano or $-N(R^1)_2$;

each R^6 is alkyl;

40 or one of R^6 together with another R^6 on different carbon atom from an alkylene bridge and the other R^6 's are each alkyl;

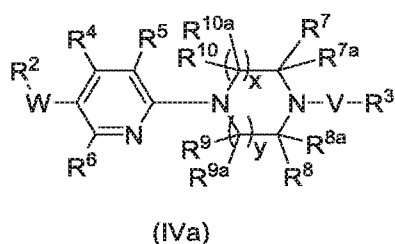
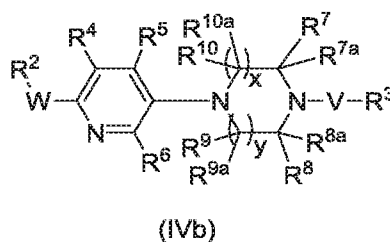
R^7 and R^{7a} are independently selected from hydrogen and alkyl;

R^8 is selected from hydrogen, alkyl, fluoro, chloro, methoxy, trifluoromethyl, cyano, nitro or $-N(R^1)_2$; and

R^9 is selected from hydrogen, alkyl, fluoro or chloro.

Compounds of Formula (III) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2006/125181, WO2007/046868, and WO2006/125194. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2006/125181, WO2007/046868, and WO2006/125194, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula IVa-IVb:



wherein:

each R^1 is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} hydroxyalkyl, C_4 - C_{12} cycloalkylalkyl and C_7 - C_{19} aralkyl;

R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl;

or R^3 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^7 , R^{7a} , R^8 , R^{8a} , R^9 , R^{9a} , R^{10} , and R^{10a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

or R^7 and R^{7a} together, or R^8 and R^{8a} together, or R^9 or R^{9a} together, or R^{10} and R^{10a} together are an oxo group, provided that when V is $-C(O)-$, R^7 and R^{7a} together or R^8 and R^{8a} together do not form an oxo group, while the remaining R^7 , R^{7a} , R^8 , R^{8a} , R^9 , R^{9a} , R^{10} and R^{10a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

or one of R^{10} , R^{10a} , R^7 and R^{7a} together with one of R^8 , R^{8a} , R^9 and R^{9a} form an alkylene bridge, while the remaining R^{10} , R^{10a} , R^7 , R^{7a} , R^8 , R^{8a} , R^9 and R^{9a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

R^{11} is a hydrogen or C_1 - C_3 alkyl; and

each R¹³ is independently selected from hydrogen or C₁-C₆alkyl; or

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prod rug thereof.

In some embodiments of the compound of Formula IVa,

W is -O-, -N(R¹)-, -C(R¹)₂-, -C(O)-, -OC(O)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_t- (where t is 1 or 2), -S(O)₂N(R¹)-, -C(O)N(R¹)-, -C(S)N(R¹)-, -OS(O)₂N(R¹)-, -OC(O)N(R¹)-, -OC(S)N(R¹)-, -N(R¹)C(O)N(R¹)- or -N(R¹)C(S)N(R¹)-;

V is -C(O)-, -C(S)-, -C(O)N(R¹)-, -C(O)O-, -C(S)O-, -S(O)_t- (where t is 1 or 2), -S(O)_tN(R¹)- (where t is 1 or 2) or -C(R¹¹)H;

R⁴, R⁵, and R⁶ are each independently selected from hydrogen, bromo, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro, or -N(R¹³)₂;

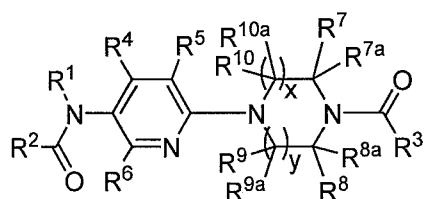
In some embodiments of the compound of Formula IVb,

W is -O-, -N(R¹)-, -C(O)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -OS(O)₂N(R¹)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -C(S)N(R¹)-, -OC(S)N(R¹)-, -N(R¹)C(O)-, -N(R¹)C(O)N(R¹)-;

V is -C(O)-, -C(S)-, -C(O)N(R¹)-, -C(O)O-, -S(O)₂-, -S(O)₂N(R¹)- or -C(R¹¹)H-;

R⁴, R⁵, and R⁶ are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro, or -N(R¹³)₂;

In some embodiments, the disclosure provides compounds of Formula (IVa) having the following Formula (IVca):



(IVca)

wherein:

R² is selected from the group consisting of C₇-C₁₂alkyl, C₃-C₁₂alkenyl, C₇-C₁₂hydroxyalkyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂hydroxyalkenyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, C₁₃-C₁₉aralkyl, C₁-C₁₂heteroaryl, C₃-C₁₂heterocyclylalkyl, C₃-C₁₂heterocyclyl, and C₃-C₁₂heteroarylalkyl, provided that R² is not pyrazinyl, pyridinonyl, pyrrolidinonyl or imidazolyl;

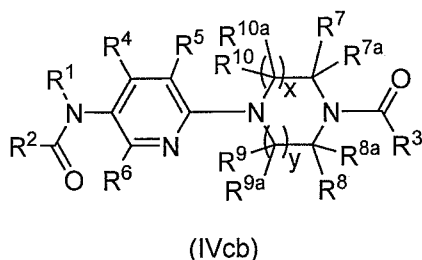
or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of C₃-C₁₂alkyl, C₃-C₁₂alkenyl, C₃-C₁₂hydroxyalkyl, C₃-C₁₂hydroxyalkenyl, C₃-C₁₂alkoxy, C₃-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

or R⁹ or R^{9a} together, or R¹⁰ and R^{10a} together form an oxo group, while the remaining R⁷, R^{7a}, R⁸, R^{8a}, R⁹, R^{9a}, R¹⁰ and R^{10a} are each independently selected from hydrogen or C₁-C₃alkyl;

In some embodiments, the disclosure provides compounds of Formula IVa having the following Formula IVcb:



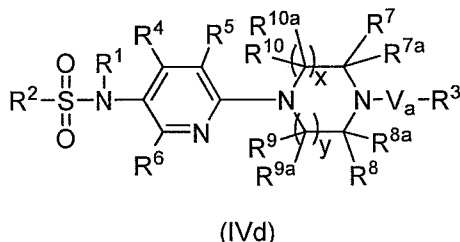
wherein:

- 5 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_6 alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl; or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the
- 10 rings may be fused to each other;

R^3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C_1 - C_6 alkyl, C_1 - C_6 trihaloalkyl, C_1 - C_6 trihaloalkoxy, C_1 - C_6 alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

- 15 or R^9 or R^{9a} together, or R^{10} and R^{10a} together form an oxo group, while the remaining R^7 , R^{7a} , R^8 , R^{8a} , R^9 , R^{9a} , R^{10} and R^{10a} are each independently selected from hydrogen or C_1 - C_3 alkyl; and each R^{12} is independently selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, aryl or aralkyl.

In some embodiments, the disclosure provides compounds of Formula IVa having the following Formula IVd:

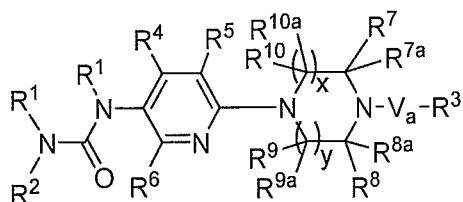


wherein:

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(S)N(R^1)-$, $-C(O)O-$, $-C(S)O-$, $-S(O)_t-$ (where t is 1 or 2), or $-S(O)_tN(R^1)-$ (where t is 1 or 2);

- 25 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_6 alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl; or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the
- 30 rings may be fused to each other.

In some embodiments, the disclosure provides compounds of Formula IVa having the following Formula IVe:



(IVe)

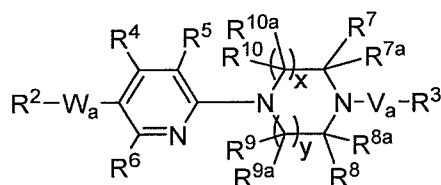
wherein:

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(S)N(R^1)-$, $-C(O)O-$, $-C(S)O-$, $-S(O)_t-$ (where t is 1 or 2), or $-S(O)_tN(R^1)-$ (where t is 1 or 2);

5 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the
10 rings may be fused to each other.

In some embodiments, the disclosure provides compounds of Formula IVa having the following Formula IVf:



(IVf)

wherein:

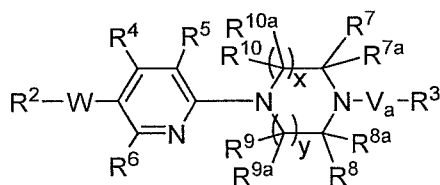
15 W_a is $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2);

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(S)N(R^1)-$, $-C(O)O-$, $-C(S)O-$, $-S(O)_t-$ (where t is 1 or 2), or $-S(O)_tN(R^1)-$ (where t is 1 or 2);

R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl,
20 C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other.

In some embodiments, the disclosure provides compounds of Formula IVa having the following
25 Formula IVaa:



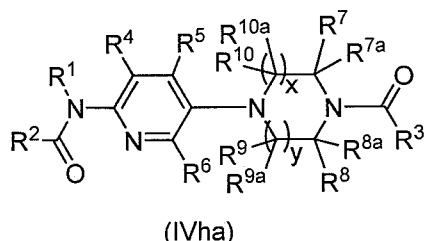
(IVaa)

wherein:

W is $-N(R^1)S(O)_t-$ (where t is 1 or 2);

V is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(S)N(R^1)-$, $-C(O)O-$, $-C(S)O-$, $-S(O)_t-$ (where t is 1 or 2), $-S(O)_tN(R^1)-$ (where t is 1 or 2) or $-C(R^{11})H$.

- 5 In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVha:



(IVha)

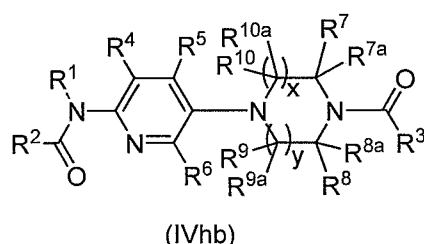
wherein:

- 10 R^2 is selected from the group consisting of C_7 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_7 - C_{12} hydroxyalkyl, C_1 - C_{12} alkoxy, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_{13} - C_{19} aralkyl, C_1 - C_{12} heteroaryl, C_3 - C_{12} heterocyclalkyl and C_3 - C_{12} heteroarylalkyl, provided that R^2 is not pyrazinyl, pyridinonyl, pyrrolidinone or imidazolyl;

- 15 or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocycl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

- 20 R^3 is selected from the group consisting of C_3 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_3 - C_{12} hydroxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocycl, C_3 - C_{12} heterocyclalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl; or R^9 or R^{9a} together, or R^{10} and R^{10a} together form an oxo group, while the remaining R^7 , R^{7a} , R^8 , R^{8a} , R^9 , R^{9a} , R^{10} and R^{10a} are each independently selected from hydrogen or C_1 - C_3 alkyl.

In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVhb:



(IVhb)

wherein:

- 25 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_6 alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocycl, C_3 - C_{12} heterocyclalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl; or R^2 is phenyl optionally substituted with one or more substituents selected from halo and C_1 - C_6 trihaloalkyl;

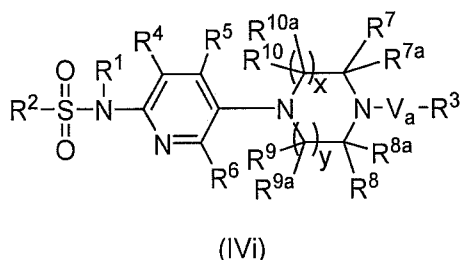
- 30 or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocycl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

R^3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 trihaloalkyl, C_1 - C_6 trihaloalkoxy, C_1 - C_6 alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

- 5 or R^9 or R^{9a} together, or R^{10} and R^{10a} together form an oxo group, while the remaining R^7 , R^{7a} , R^8 , R^{8a} , R^9 , R^{9a} , R^{10} and R^{10a} are each independently selected from hydrogen or C_1 - C_3 alkyl;
each R^{12} is independently selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, aryl or aralkyl.

In some embodiments, the disclosure provides compounds of Formula IVb having the following

- 10 Formula IVi:

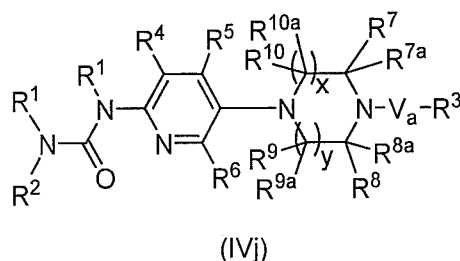


wherein:

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^1)-$;

- 15 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_6 alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other.

- 20 In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVj:



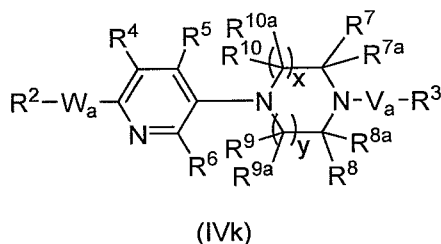
wherein:

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^1)-$;

- 25 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other.

- 30

In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVk:



wherein:

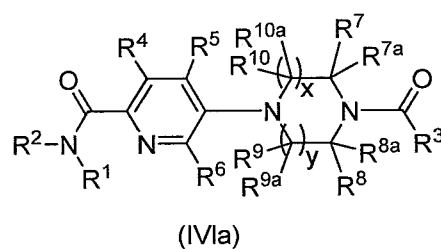
5 W_a is $-O-$, $-N(R^1)-$ or $-S(O)_t-$ (where t is 0, 1 or 2);

V_a is $-C(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^1)-$;

R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

10 or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other.

In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVla:



wherein:

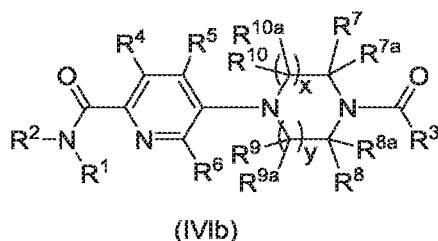
R^2 is selected from the group consisting of C_7 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_7 - C_{12} hydroxyalkyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_{13} - C_{19} aralkyl, C_3 - C_{12} heterocyclalkyl, and C_3 - C_{12} heteroarylalkyl;

20 or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

R^3 is selected from the group consisting of C_3 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_3 - C_{12} hydroxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_5 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl;

25 or R^3 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other.

30 In some embodiments, the disclosure provides compounds of Formula IVb having the following Formula IVlb:



wherein:

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₃-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

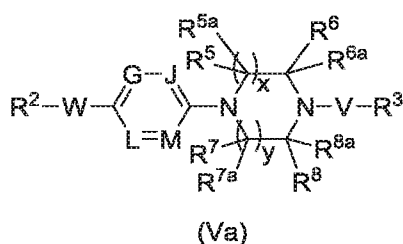
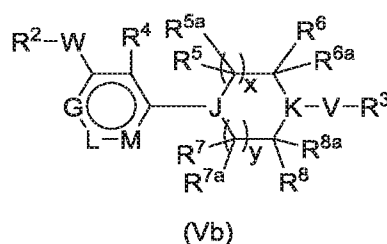
or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is naphthyl or phenyl, each optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C₁-C₆alkyl, C₁-C₆trihaloalkyl, C₁-C₆trihaloalkoxy, C₁-C₆alkylsulfonyl, -N(R¹²)₂, -OC(O)R¹², -C(O)OR¹², -S(O)₂N(R¹²)₂, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R³ is not phenyl substituted with optionally substituted thienyl, and provided that when R³ is naphthyl, R² cannot be C₁-C₆alkyl, C₂-C₆hydroxyalkyl or phenyl substituted by amino;

each R¹² is independently selected from hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, aryl or aralkyl.

Compounds of Formula (IV) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2005/011656 and WO2005/011654. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2005/011656 and WO2005/011654, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula V:



wherein:

each R¹ is independently selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂hydroxyalkyl, C₄-C₁₂cycloalkylalkyl and C₇-C₁₉aralkyl;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} is independently selected from hydrogen or C₁-C₃alkyl;

or R⁵ and R^{5a} together, or R⁶ and R^{6a} together, or R⁷ and R^{7a} together, or R⁸ and R^{8a} together are an oxo group, provided that when V is -C(O)-, R⁶ and R^{6a} together or R⁸ and R^{8a} together do not form an oxo group, while the remaining R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

5 each R⁹ is independently selected from hydrogen or C₁-C₆alkyl.

In some embodiments of the compound of Formula Va,

x and y are each independently 1, 2 or 3;

G, J, L and M are each independently selected from -N= or -C(R⁴)=; provided that at most two of G, J, L and M are -N=;

10 V is -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(R¹⁰)H-, -N(R¹)-, -C(=NR^{1a})-, or -O-;

W is a direct bond, -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_p- (where p is 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(O)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-, -NR¹C(=NR^{1a})NR¹-, -NR¹C(=S)NR¹-, or -C(=NR^{1a})NR¹-;

15 each R^{1a} is independently selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₄-C₁₂cycloalkylalkyl, C₇-C₁₉aralkyl, OR¹, and cyano;

R³ is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

20 or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R⁴ is independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or -N(R⁹)₂;

25 or one of R⁵, R^{5a}, R⁶, and R^{6a} together with one of R⁷, R^{7a}, R⁸ and R^{8a} form an alkylene bridge, while the remaining R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

R¹⁰ is hydrogen or C₁-C₃alkyl;

30 provided that when G, J and L are each -C(R⁴) where each R⁴ is hydrogen, and M is -N=, and x is 1 or 2 and y is 1; W cannot be -N(R¹)C(O)-;

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula Vb,

x and y are each independently 0, 1, 2 or 3;

G is -N= or -C(R⁴)=;

35 J and K are each independently N or C(R¹⁰);

L and M are each independently -N= or -C(R⁴)=; provided that L and M cannot both be -C(R⁴)= when G is -C(R⁴)= and provided that L and M cannot both be -N= when G is -N=;

V is a direct bond, -N(R¹)-, -N(R¹)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_p- (where p is 0, 1 or 2) or -S(O)_pN(R¹)- (where p is 1 or 2);

40 W is a direct bond, -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)_p- (where p is 1 or 2), -S(O)_pN(R¹)- (where p is 1 or 2), -C(O)-,

-OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-;

R³ is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl;

5 or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R⁴ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, haloalkyl, cyano, nitro or -N(R⁹)₂;

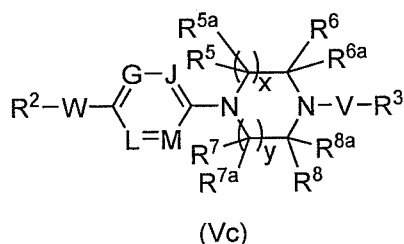
10 or one of R⁵, R^{5a}, R⁶, and R^{6a} together with one of R⁷, R^{7a}, R⁸ and R^{8a} forms a direct bridge or an alkylene bridge, while the remaining R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy;

as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a

15 pharmaceutically acceptable salt thereof, or as a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula Va having the following Formula Vc:



wherein:

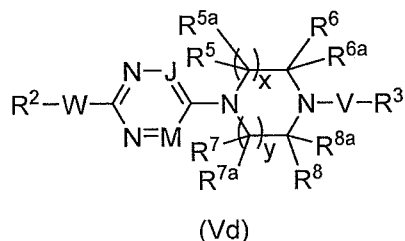
20 W is -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -C(O)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O- or -N(R¹)C(O)O-;

V is -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)₂-, -S(O)₂N(R¹)-, -C(R¹⁰)H-;

G, J, L and M are each independently selected from -N= or -C(R⁴)=; provided that at least two of G, J, L and M are -N=, and provided that when G and J are both -C(R⁴)=, L and M cannot both be -N=, and when L and M are both -C(R⁴)=, G and J cannot both be -N=;

25 a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula Va having the following Formula Vd:



wherein:

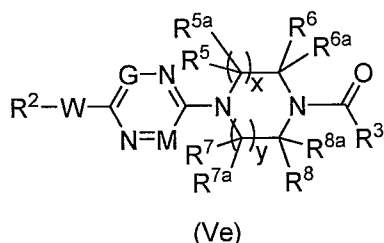
W is $-N(R^1)C(O)-$, $-C(O)N(R^1)-$, $-OC(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$, $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-N(R^1)S(O)_2-$, $-S(O)_2N(R^1)-$, $-C(O)-$, $-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$ or $-N(R^1)C(O)O-$;

V is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-C(O)N(R^1)-$, $-S(O)_2-$, $-S(O)_2N(R^1)-$, $-C(R^{10})H-$;

J and M are each independently selected from $-N=$ or $-C(R^4)=$;

- 5 a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula Va having the following Formula Ve:



- 10 wherein:

W is $-N(R^1)C(O)-$, $-C(O)N(R^1)-$ or $-OC(O)N(R^1)-$;

G and M are each $-C(R^4)=$;

R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

- 15 or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

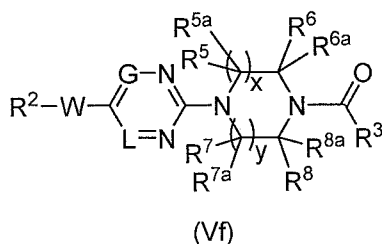
R^3 is phenyl optionally substituted by one or more substituents selected from the group of halo, cyano, nitro, hydroxy, C_1 - C_6 alkyl, C_1 - C_6 trihaloalkyl, C_1 - C_6 trihaloalkoxy, C_1 - C_6 alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroaryl/cycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

- 20 each R^5 , R^{5a} , R^6 , R^{6a} , R^7 , R^{7a} , R^8 and R^{8a} is independently selected from hydrogen or C_1 - C_3 alkyl; or R^5 and R^{5a} together or R^7 and R^{7a} together form an oxo group, while the remaining R^5 , R^{5a} , R^6 , R^{6a} , R^7 , R^{7a} , R^8 and R^{8a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

- 25 each R^{12} is independently selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, aryl or aralkyl; a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula Va having the following

- 30 Formula Vf:



wherein:

W is -N(R¹)C(O)-, -C(O)N(R¹)- or -OC(O)N(R¹)-;

G and L are each -C(R⁴)=;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₃-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is phenyl optionally substituted by one or more substituents selected from the group of halo, cyano, nitro, hydroxy, C₁-C₆alkyl, C₁-C₆trihaloalkyl, C₁-C₆trihaloalkoxy, C₁-C₆alkylsulfonyl, -N(R¹²)₂, -OC(O)R¹², -C(O)OR¹², -S(O)₂N(R¹²)₂, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R³ is not phenyl substituted with optionally substituted thienyl;

each R⁵, R^{5a}, R⁶, R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} is independently selected from hydrogen or C₁-C₃alkyl; or R⁵ and R^{5a} together or R⁷ and R^{7a} together form an oxo group, while the remaining R⁵, R^{5a}, R⁶,

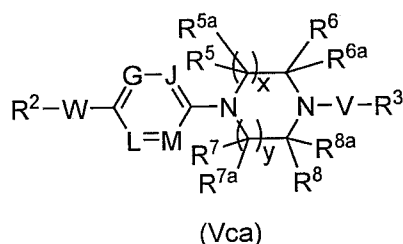
R^{6a}, R⁷, R^{7a}, R⁸ and R^{8a} are each independently selected from hydrogen or C₁-C₃alkyl;

each R¹² is independently selected from hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, aryl or aralkyl;

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula Va having the following

Formula Vca:



wherein:

W is -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -C(O)O- or -N(R¹)C(O)O-;

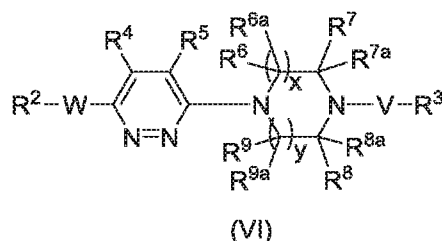
V is -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)₂-, -S(O)₂N(R¹)-;

G, J, L and M are each independently selected from -N= or -C(R⁴)=; provided that at least two of G, J, L and M are -N=, and provided that when G and J are both -C(R⁴)=, L and M cannot both be -N=, and when L and M are both -C(R⁴)=, G and J cannot both be -N=;

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

Compounds of Formula (V) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2006/086445, WO2006/034446 and WO2005/011657. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2006/086445, WO2006/034446 and WO2005/011657, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula VI:



wherein:

5 x and y are each independently 1, 2 or 3;

W is -C(O)N(R¹)-, -C(O)N[C(O)R^{1a}]-, -N(R¹)C(O)N(R¹)- or -N(R¹)C(O)-;

V is -C(O)-, -C(S)-, -C(R¹⁰)H-;

each R¹ is independently selected from the group consisting of hydrogen; C₁-C₆alkyl optionally substituted with one or more substituents selected from the group consisting of halo, methyl or trifluoromethyl; and C₂-C₆alkyl optionally substituted with one or more substituents selected from the group consisting of methoxy and hydroxyl;

R^{1a} is selected from the group consisting of hydrogen, C₁-C₆alkyl and cycloalkyl;

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₁-C₁₂alkoxy, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl; or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₁-C₁₂alkoxy, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₂aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl; or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R⁴ and R⁵ are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or -N(R¹²)₂;

R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are each independently selected from hydrogen or C₁-C₃alkyl;

or R⁶ and R^{6a} together, or R⁷ and R^{7a} together, or R⁸ and R^{8a} together, or R⁹ and R^{9a} together are an oxo group, provided that when V is -C(O)-, R⁷ and R^{7a} together or R⁸ and R^{8a} together do not form an oxo group, while the remaining R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are each independently selected from hydrogen or C₁-C₃alkyl;

or one of R⁶, R^{6a}, R⁷ and R^{7a} together with one of R⁸, R^{8a}, R⁹ and R^{9a} form an alkylene bridge, while the remaining R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are each independently selected from hydrogen or C₁-C₃alkyl;

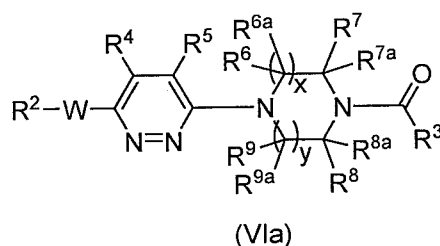
R¹⁰ is hydrogen or C₁-C₃alkyl; and

each R^{12} is independently selected from hydrogen or C_1 - C_6 alkyl;

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

In some embodiments, the disclosure provides compounds of Formula VI having the following

5 Formula VIa:



wherein:

W is $-C(O)N(R^1)-$ or $-N(R^1)C(O)-$;

10 R^2 is selected from the group consisting of C_7 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_7 - C_{12} hydroxyalkyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, C_{13} - C_{19} aralkyl, C_3 - C_{12} heterocyclalkyl, and C_3 - C_{12} heteroarylalkyl;

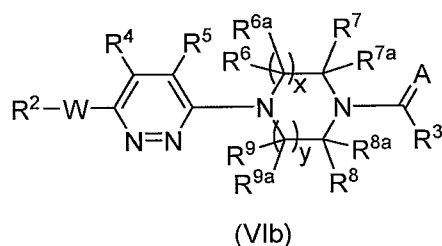
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocycl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

15 R^3 is selected from the group consisting of C_3 - C_{12} alkyl, C_3 - C_{12} alkenyl, C_3 - C_{12} hydroxyalkyl, C_3 - C_{12} hydroxyalkenyl, C_3 - C_{12} alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{12} aralkyl, C_3 - C_{12} heterocycl, C_3 - C_{12} heterocyclalkyl, C_5 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl;

or R^3 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocycl, aryl and heteroaryl and where some or all of the
20 rings may be fused to each other;

R^4 and R^5 are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, and trifluoromethyl.

In some embodiments, the disclosure provides compounds of Formula VI having the following
Formula VIb:



25 wherein:

A is oxygen or sulfur;

W is $-C(O)N(R^1)-$ or $-N(R^1)C(O)-$;

30 R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_6 alkoxy, C_3 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{12} aralkyl, C_3 - C_{12} heterocycl, C_3 - C_{12} heterocyclalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

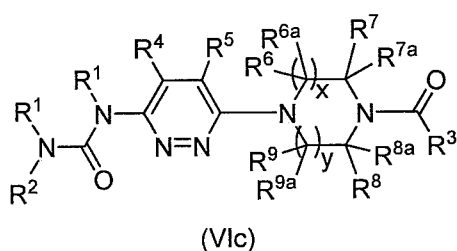
or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C₁-C₆alkyl, C₁-C₆trihaloalkyl, C₁-C₆trihaloalkoxy, C₁-C₆alkylsulfonyl, -N(R¹¹)₂, -OC(O)R¹¹, -C(O)OR¹¹, -S(O)₂N(R¹¹)₂, cycloalkyl, heterocyclyl, heteroaryl and heteroaryl/cycloalkyl, provided that R³ is not phenyl substituted with optionally substituted thienyl;

R⁴ and R⁵ are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, and trifluoromethyl.

each R¹¹ is independently selected from hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, aryl or aralkyl.

In some embodiments, the disclosure provides compounds of Formula VI having the following Formula VIc:



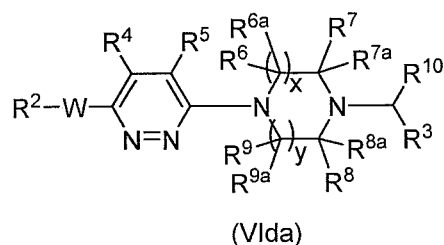
wherein:

R² is selected from the group consisting of C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, aryl, C₇-C₁₉aralkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R⁴ and R⁵ are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, and trifluoromethyl.

In some embodiments, the disclosure provides compounds of Formula VI having the following Formula VIa:



wherein:

W is -C(O)N(R¹)-, -N(R¹)C(O)N(R¹)- or -N(R¹)C(O)-;

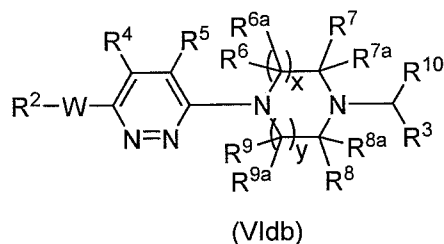
R² is selected from the group consisting of C₇-C₁₂alkyl, C₂-C₁₂alkenyl, C₇-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₁-C₁₂alkoxy, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, C₁₃-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl, and C₃-C₁₂heteroarylalkyl;

R¹⁰ is hydrogen or C₁-C₃alkyl; and

each R^{12} is independently selected from hydrogen or C_1 - C_6 alkyl;

provided, however, that R^2 cannot be pyrazinyl, pyridinonyl, pyrrolidinonyl or imidazolyl.

In some embodiments, the disclosure provides compounds of Formula VI having the following Formula VIb:



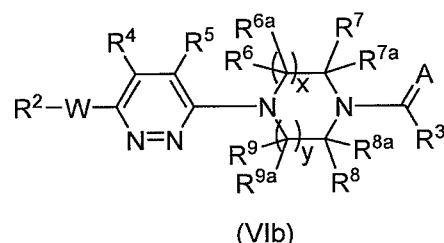
5

wherein:

W is $-C(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$ or $-N(R^1)C(O)-$;

R^3 is selected from the group consisting of C_7 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_1 - C_{12} alkoxy or C_2 - C_{12} alkoxyalkyl.

10 In some embodiments, the disclosure provides compounds of Formula VI having the following Formula VIe:



wherein:

W is a direct bond, $-C(O)N(R^1)-$, $-C(O)N[C(O)R^{1a}]-$, $-N(R^1)C(O)N(R^1)-$, $-N(R^1)C(O)-$,

15 $-OC(O)N(R^1)-$, $-N(R^1)S(O)_p-$ (where p is 1 or 2), $-S(O)_pN(R^1)-$ (where p is 1 or 2), $-C(O)-$, $-OS(O)_2N(R^1)-$, $-O(C)O-$, $-C(O)O-$, $-N(R^1)C(O)O-$, $-N(R^1)C(=NR^{1a})N(R^1)-$, $-N(R^1)C(=S)N(R^1)-$, $-N(R^1)C(=NR^{1a})-$, or $-C(=NR^{1a})N(R^1)-$;

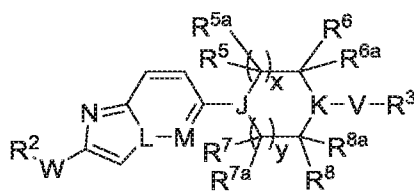
V is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-C(O)N(R^1)-$, $-S(O)_t-$ (where t is 0, 1, or 2), $-S(O)_pN(R^1)-$ (where p is 1 or 2), $-C(R^{10})H-$ or $-C(=NR^{1a})-$;

20 R^{1a} is selected from the group consisting of hydrogen, $-OR^1$, cyano, C_1 - C_6 alkyl and cycloalkylalkyl.

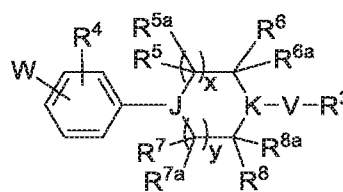
Compounds of Formula (VI) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2005/011655, WO2006/086447 and WO2009/106991. In some

25 embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2005/011655, WO2006/086447 and WO2009/106991, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula VII:



(VIIa)



(VIIb)

wherein:

each R^1 is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} hydroxyalkyl, C_4 - C_{12} cycloalkylalkyl and C_7 - C_{19} aralkyl;

R^2 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl, and C_3 - C_{12} heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^5 , R^{5a} , R^6 , R^{6a} , R^7 , R^{7a} , R^8 and R^{8a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

or R^5 and R^{5a} together, R^6 and R^{6a} together, or R^7 and R^{7a} together, or R^8 and R^{8a} together are an oxo group, provided that when V is $-C(O)-$, R^6 and R^{6a} together or R^8 and R^{8a} together do not form an oxo group, while the remaining R^5 , R^{5a} , R^6 , R^{6a} , R^7 , R^{7a} , R^8 and R^{8a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

or one of R^5 , R^{5a} , R^6 and R^{6a} together with one of R^7 , R^{7a} , R^8 and R^{8a} forms a direct bond or an alkylene bridge, while the remaining R^5 , R^{5a} , R^6 , R^{6a} , R^7 , R^{7a} , R^8 and R^{8a} are each independently selected from hydrogen or C_1 - C_3 alkyl;

each R^9 is independently selected from hydrogen or C_1 - C_6 alkyl;

as a stereoisomer, enantiomer or tautomer thereof, as a mixture of stereoisomers, as a pharmaceutically acceptable salt thereof, or as a prodrug thereof.

In some embodiments of the compound of Formula VIIa,

x and y are each independently 1, 2 or 3;

J and K are each independently N or $C(R^1)$;

L is N or $C(R^4)$;

M is $-N=$ or $-C(R^4)-$;

W is a direct bond, $-N(R^1)C(O)-$, $-C(O)N(R^1)-$, $-OC(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$, $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-N(R^1)S(O)_p-$ (where p is 1 or 2), $-S(O)_pN(R^1)-$ (where p is 1 or 2), $-C(O)-$, $-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$, $-N(R^1)C(O)O-$ or $-C(R^1)_2-$;

V is $-N(R^1)-$, $-N(R^1)C(O)-$, $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-C(O)N(R^1)-$, $-S(O)_p-$ (where p is 0, 1 or 2) or $-S(O)_pN(R^1)-$ (wherein p is 1 or 2) or $-C(R^{10})H$;

R^3 is selected from the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} hydroxyalkyl, C_2 - C_{12} hydroxyalkenyl, C_2 - C_{12} alkoxyalkyl, C_3 - C_{12} cycloalkyl, C_4 - C_{12} cycloalkylalkyl, aryl, C_7 - C_{19} aralkyl, C_3 - C_{12} heterocyclyl, C_3 - C_{12} heterocyclylalkyl, C_1 - C_{12} heteroaryl and C_3 - C_{12} heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R⁴ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, haloalkyl, cyano, nitro or -N(R⁹)₂;

R¹⁰ is a hydrogen or C₁-C₃alkyl; and

R¹¹ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy;

In some embodiments of the compound of Formula VIIb,

x and y are each independently 0, 1, 2 or 3;

J and K are each independently N or C(R¹⁰);

V is a direct bond, -N(R¹)-, -N(R¹)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_p- (where p is 0, 1 or 2) or -S(O)_pN(R¹)- (where p is 1 or 2);

W is R²-N(R¹)C(O)-, R²-C(O)N(R¹)-, R²-OC(O)N(R¹)-, R²-N(R¹)C(O)N(R¹)-, R²-O-, R²-N(R¹)-, R²-S(O)_t- (where t is 0, 1 or 2), R²-N(R¹)S(O)_p- (where p is 1 or 2), R²-S(O)_pN(R¹)- (where p is 1 or 2),

R²-C(O)-, R²-OS(O)₂N(R¹)-, R²-OC(O)-, R²-C(O)O-, R²-N(R¹)C(O)O- or R²-C(R¹)₂-;

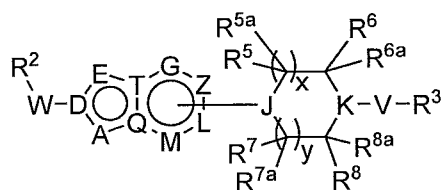
R³ is selected from the group consisting of hydrogen, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₁₂hydroxyalkyl, C₂-C₁₂hydroxyalkenyl, C₂-C₁₂alkoxyalkyl, C₃-C₁₂cycloalkyl, C₄-C₁₂cycloalkylalkyl, aryl, C₇-C₁₉aralkyl, C₃-C₁₂heterocyclyl, C₃-C₁₂heterocyclylalkyl, C₁-C₁₂heteroaryl and C₃-C₁₂heteroarylalkyl, provided that R³ is not optionally substituted cyclopentyl or an optionally substituted 5-membered heterocyclic ring;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R⁴ is hydrogen, fluoro, chloro, hydroxyl, C₁-C₁₂alkyl, C₁-C₁₂alkoxy, haloalkyl, cyano, nitro or -N(R⁹)₂;

each R¹⁰ is independently selected from hydrogen, fluoro, chloro, C₁-C₁₂alkyl or C₁-C₁₂alkoxy.

In some embodiments, the disclosure provides compounds of Formula VIIa having the following Formula VIIc:

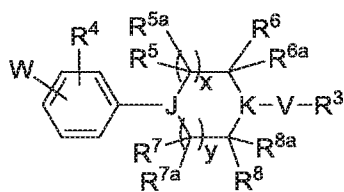


(VIIc)

A, D, E, G, Z, L, and M are each independently N, NH or C(R⁴);

T and Q are each independently C or N.

In some embodiments, the disclosure provides compounds of Formula VIIb having the following Formula VIId:



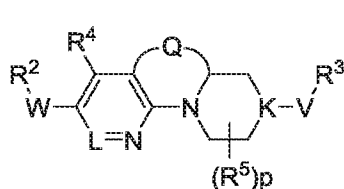
(VIIId)

W is -CN, R²-N(R¹)C(O)-, R²-C(O)N(R¹)-, R²-OC(O)N(R¹)-, R²-N(R¹)C(O)N(R¹)-, R²-O-, R²-N(R¹)-, R²-S(O)_t- (where t is 0, 1 or 2), R²-N(R¹)S(O)_p- (where p is 1 or 2), R²-S(O)_pN(R¹)- (where p is 1 or 2), R²-C(O)-, R²-OS(O)₂N(R¹)-, R²-OC(O)-, R²-C(O)O-, R²-N(R¹)C(O)O- or R²-C(R¹)₂-.

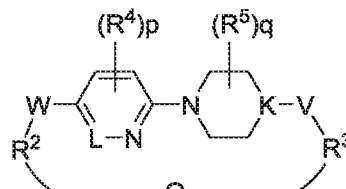
5 Compounds of Formula (VII) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2006/034312 and WO2006/034441. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2006/034312 and WO2006/034441, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of

10 Formula VIII:



(VIIIa)



(VIIIb)

wherein:

K is selected from N or C(R⁶);

L is -N= or -C(R⁴)=;

15 each R¹ is independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, cycloalkylalkyl and aralkyl;

each R⁵ is alkyl;

or one of R⁵ together with one of R⁵ on a different carbon atom form an alkylene bridge, while the remaining R⁵'s are each alkyl;

20 R⁶ is hydrogen, alkyl, fluoro or chloro; and

R⁷ is hydrogen, alkyl, fluoro, chloro, methoxy, trifluoromethyl, cyano, nitro or -N(R¹)₂;

or a stereoisomer, enantiomer or tautomer thereof, or a racemic or non-racemic mixture thereof, or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments of the compound of Formula VIIIa,

25 p is 0 to 7;

Q is an optionally substituted alkylene bridge or -(CH₂)_xA(CH₂)_y- where x and y are independently selected from 0, 1, 2, or 3 and A is selected from -O-, -C(O)-, -N(R¹)-, -N(R¹)C(O)-, -C(O)N(R¹)-, -S(O)_t- (where t is 0, 1 or 2);

30 W is -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -C(O)-, -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-,

-N(R¹)C(NR^{1a})N(R¹)-, -N(R¹)C(S)N(R¹)-, -N(R¹)C(NR^{1a})-, -C(NR^{1a})N(R¹)-, heteroaryl, heterocyclyl or a direct bond;

when K is C(R⁶), V is -O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -C(O)N(R¹)-, -N(R¹)C(O)-, -S(O)_t- (where t is 0, 1 or 2), -S(O)_qN(R¹)- (where q is 1 or 2), -N(R¹)S(O)_q- (where q is 1 or 2), -C(R⁷)H- or
 5 -C(NR^{1a})-;

each R^{1a} is selected from the group consisting of hydrogen, C₁-C₆alkyl, cycloalkylalkyl, -OR¹ and cyano;

R² is selected from the group consisting of alkylene, cycloalkyl, aryl, heterocyclyl, and heteroaryl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected
 10 from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected
 15 from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R⁴ is hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or -N(R¹)₂.

In some embodiments of the compound of Formula VIIIb,

p is 0 to 2;

q is 0 to 8;

W is -N(R¹)C(O)-, -C(O)N(R¹)-, -OC(O)N(R¹)-, -N(R¹)C(O)N(R¹)-, -O-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -C(O)-, -N(R¹)S(O)₂-, -S(O)₂N(R¹)-, -OS(O)₂N(R¹)-, -OC(O)-, -C(O)O-, -N(R¹)C(O)O-,
 -NR¹C(=NR^{1a})NR¹-, -NR¹C(=S)NR¹-, -NR¹(R^{1a})N-C-, or -C(=NR^{1a})NR¹-, a heteroaryl group, a heterocyclyl
 20 group or a direct bond;

V is -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -S(O)_pN(R¹)- (where p is 1
 25 or 2), -C(R⁷)H- or -C(=NR^{1a})-;

Q is an optionally substituted C₈-C₂₀alkylene bridge, or -(CH₂)_xA(CH₂)_y- where x and y are independently selected from 0 to 10 provided that the sum of x and y is 8 to 20, and A is selected from
 -O-, -C(O)-, -N(R¹)C(O)-, -C(O)N(R¹)-, -N(R¹)-, -S(O)_t- (where t is 0, 1 or 2), -S(O)_pN(R¹)- (where p is 1 or
 30 2), aryl, heterocyclyl, or heteroaryl;

R^{1a} is selected from the group consisting of hydrogen, C₁-C₆alkyl and cycloalkylalkyl, -OR¹, nitro, -S(O)₂R^{1b}, and cyano;

R^{1b} is C₁-C₆alkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected
 35 from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

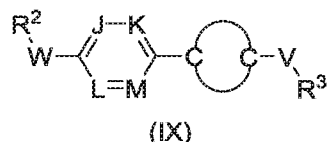
R³ is selected from the group consisting of cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl;

or R³ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected
 40 from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

each R^4 is independently selected from alkyl, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro or $-N(R^1)_2$.

Compounds of Formula (VIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2006/125179 and WO2007/136746. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2006/125179 and WO2007/136746, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula IX:



wherein:

W is $-N(R^1)C(O)-$, $-C(O)N(R^1)-$, $-OC(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$, $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-C(O)-$, $-N(R^1)S(O)_2-$, $-S(O)_2N(R^1)-$, $-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$, $-N(R^1)C(O)O-$, $-N(R^1)C(NR^{1a})N(R^1)-$, $-N(R^1)C(S)N(R^1)-$, $-N(R^1)C(NR^{1a})-$, $-C(NR^{1a})N(R^1)-$, heteroaryl, heterocyclyl or a direct bond;

V is $-O-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-C(O)N(R^1)-$, $-N(R^1)C(O)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-S(O)_qN(R^1)-$ (where q is 1 or 2), $-N(R^1)S(O)_q-$ (where q is 1 or 2), $-C(R^5)H-$ or $-C(NR^{1a})-$;



is selected from cycloalkyl, aryl, heterocyclyl, or heteroaryl;

J, K, L and M are independently selected from $-N=$ or $-C(R^4)=$;

each R^1 is independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, cycloalkylalkyl and aralkyl;

each R^{1a} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, cycloalkylalkyl, $-OR^1$, and cyano;

R^2 is selected from the group consisting of alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is selected from the group consisting of alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

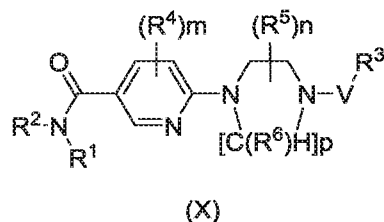
or R^3 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other; and

R^4 is selected from hydrogen, alkyl, fluoro, chloro, methoxy, trifluoromethyl, cyano, nitro or $-N(R^1)_2$;

or a stereoisomer, enantiomer or tautomer thereof, or a racemic or non-racemic mixture thereof, or a pharmaceutically acceptable salt or prodrug thereof.

Compounds of Formula (IX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/044085. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/044085, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula X,



wherein:

m is 1, 2 or 3;

n is 1, 2, 3 or 4;

p is 2, 3 or 4;

V is -C(O)-, -S(O)- or -S(O)₂;

R¹ is hydrogen, alkyl, alkenyl, aryl, heteroaryl, aralkyl, aralkenyl or cycloalkyl;

R² is selected from the group consisting of hydrogen, -R⁷-OR⁸, -R⁷-N(R⁶)₂, -R⁷-S(O)_tR¹⁰ (where t is 0, 1 or 2), alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl and optionally substituted heteroarylalkenyl;

R³ is selected from the group consisting of hydrogen, -R⁹-OR⁸, -R⁹-N(R⁶)₂, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl and optionally substituted heteroarylalkenyl;

each R⁴ is independently hydrogen, alkyl, alkenyl, halo, haloalkyl, aryl, cyano, nitro, -R⁹-OR⁸, -R⁹-N(R⁶)₂ or -S(O)_tR¹⁰ (where t is 0, 1 or 2);

each R⁵ and R⁶ is independently hydrogen, oxo, alkyl, alkenyl, halo, haloalkyl or aryl;

or one R⁵ and one R⁶ may together form an straight or branched alkylene bridge;

each R⁷ is independently a straight or branched alkylene or alkenylene chain;

each R⁸ is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

each R⁹ is independently a direct bond or a straight or branched alkylene or alkenylene chain;

and

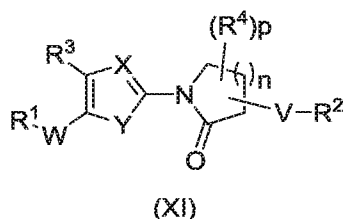
R^{10} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

as a single stereoisomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer.

- 5 Compounds of Formula (X) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2006/014168. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2006/014168, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of

- 10 Formula XI,



wherein:

X is CH or N;

Y is NH, N-CH₃, O or S;

- 15 W is selected from -N(R⁵)C(O)-, -C(O)N(R⁵)-, -OC(O)N(R⁵)-, -N(R⁵)C(O)O-, -N(R⁵)C(O)N(R⁵)-, -O-, -S-, -N(R⁵)-, -S(O)_t, -N(R⁵)S(O)_t, -S(O)_tN(R⁵)-, -OS(O)_tN(R⁵)-, C(O)-, -OC(O)-, -C(O)O-, -N(R⁵)C(=N(R^{5a}))NR⁵-, -N(R⁵)((R^{5a})N=C)-, -C(=N(R^{5a}))N(R⁵)-, or a direct bond;

V is selected from -N(R⁵)C(O)-, -C(O)N(R⁵)-, -OC(O)N(R⁵)-, -N(R⁵)C(O)O-, -N(R⁵)C(O)N(R⁵)-, -O-, -S-, -N(R⁵)-, -S(O)_t, -N(R⁵)S(O)_t, -S(O)_tN(R⁵)-, -OS(O)_tN(R⁵)-, C(O)-, -OC(O)-, -C(O)O-, -N(R⁵)C(=N(R^{5a}))NR⁵-, -N(R⁵)((R^{5a})N=C)-, -C(=N(R^{5a}))N(R⁵)-, =C(R⁵)- or a direct bond;

- 20 n is 0, 1, 2 or 3;

p is an integer from 0 to 9;

t is 1 or 2;

- 25 R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R^1 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

- 30 R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the

- 35 rings may be fused to each other;

R^3 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, haloalkoxy, cyano and $-N(R^5)_2$;

each R^4 is independently selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, alkoxy, $-N(R^5)_2$, cycloalkylalkyl and aralkyl;

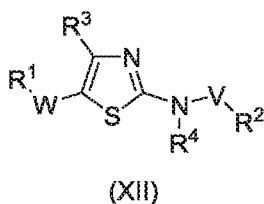
or two R^4 s attached to the same carbon form an oxo while each of the remaining R^4 s are as described above;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, hydroxyalkyl, cycloalkylalkyl and aralkyl; and

R^{5a} is selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl and cyano; or a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

Compounds of Formula (XI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/036715. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/036715, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XII,



wherein:

W is selected from $-O-$, $-OC(O)-$, $-OC(O)N(R^5)-$, $-OS(O)_2N(R^5)-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^5)-$, $-N(R^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)O-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)S(O)_2-$, $-S(O)_t-$ (where t is 0, 1 or 2), or $-S(O)_2N(R^5)-$;

V is selected from $-C(O)-$, $-C(O)N(R^5)-$, $-C(O)O-$, $-S(O)_t-$ (where t is 1 or 2) or a direct bond;

R^1 is selected from the group consisting of alkyl, alkenyl, $-R^6-OR^7$, hydroxyalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclalkyl, heteroaryl, and heteroarylalkyl; or R^1 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^2 is selected from the group consisting of alkyl, alkenyl, $-R^6-OR^7$, hydroxyalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclalkyl, heteroaryl and heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

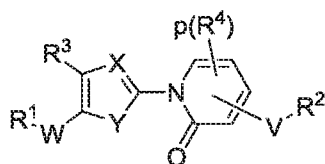
R^3 is selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, fluoro, chloro, bromo, trihaloalkyl, trihaloalkoxy, cyano, nitro, $-OR^4$, $-OC(O)R^2$, $-N(R^5)C(O)OR^5$, $-N(R^5)C(O)N(R^4)(R^5)$ or $-N(R^5)S(O)_2R^2$;

each R^4 and R^5 is independently selected from the group consisting of
 $R^6-N(R^7)_2$, $-R^6-OR^7$, $-R^6-C(O)OR^7$, hydrogen, alkyl, cycloalkylalkyl and aralkyl;
 each R^6 is a straight or branched alkylene chain; and
 each R^7 is hydrogen, alkyl, aryl or aralkyl;

or a stereoisomer, enantiomer or tautomer thereof, or a racemic or non-racemic mixture thereof,
 or a pharmaceutically acceptable salt or prodrug thereof.

Compounds of Formula (XII) may be synthesized by methods known in the art, e.g., those
 described in International Patent Publication No. WO2007/130075. In some embodiments, the SCD
 inhibitor is a compound disclosed in International Patent Publication No. WO2007/130075, the
 compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of
 Formula XIII,



(XIII)

wherein:

V is selected from $-N(R^5)C(O)-$, $-C(O)N(R^5)-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-N(R^5)C(O)N(R^5)-$,
 $-O-$, $-N(R^5)-$, $-S-$, $-S(O)-$, $-N(R^5)S(O)-$, $-S(O)N(R^5)-$, $-OS(O)_2$, $-OS(O)_2N(R^5)-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$,
 $-N(R^5)C(=N(R^{5a}))NR^5-$, $-N(R^5)C(=S)NR^5-$, $-N(R^5)((R^{5a})N=C)-$, $-C(=N(R^{5a}))N(R^5)-$, alkylene, alkenylene,
 alkynylene, aryl, heteroaryl, a cycloalkyl, a heterocyclyl, or a direct bond;

W is selected from $-N(R^5)C(O)-$, $-C(O)N(R^5)-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-N(R^5)C(O)N(R^5)-$,
 $-O-$, $-N(R^5)-$, $-S-$, $-S(O)-$, $-N(R^5)S(O)-$, $-S(O)N(R^5)-$, $-OS(O)_2N(R^5)-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$,
 $-N(R^5)C(=N(R^{5a}))NR^5-$, $-N(R^5)((R^{5a})N=C)-$, $-C(=N(R^{5a}))N(R^5)-$, aryl, a heteroaryl, heterocyclyl, alkynylene,
 alkenylene, alkylene or direct bond;

X is selected from $C(H)$ or N ;

Y is selected from S , O , $N(H)$ or $N(CH_3)$;

p is 0, 1, 2, or 3;

t is 1 or 2;

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl,
 alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and
 heteroarylalkyl;

or R^1 is a multi-rings structure having 2 to 4 rings wherein the rings are independently selected
 from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the
 rings may be fused to each other;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl,
 alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl
 and heteroarylalkyl;

or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, trihaloalkoxy, cyano and $-N(R^5)_2$;

R^4 is selected from the group consisting of alkyl, hydroxyalkyl, cycloalkylalkyl, aralkyl, halo, haloalkyl, $-OCF_3$, $-OC(H)F_2$, and cyano;

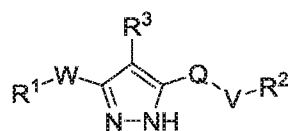
or two adjacent R^4 groups, together with the carbon atoms to which they are attached, may form a cycloalkyl, heterocyclyl, aryl or heteroaryl and the remaining R^4 groups, if present, are as described above;

R^5 is selected from the group consisting of hydrogen, aryl, alkyl, heteroaryl, heterocyclyl, haloalkyl, hydroxyalkyl, cycloalkylalkyl and aralkyl;

R^{5a} is selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl and cyano; a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

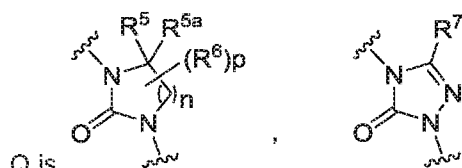
Compounds of Formula (XIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/143597. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/143597, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XIV,



(XIV)

wherein:



W is $-N(R^8)C(O)-$, $-C(O)N(R^8)-$, C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene or a direct bond;

V is selected from a C_1-C_8 alkylene;

n is 1, 2, or 3;

p is 1, 2, 3, 5, or 6;

R^1 is hydrogen, an optionally substituted C_1-C_7 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, hydroxy C_1-C_4 alkyl, C_1-C_7 alkoxy C_1-C_4 alkyl, an optionally substituted C_3-C_7 cycloalkyl, an optionally substituted C_3-C_7 cycloalkyl C_1-C_4 alkyl, an optionally substituted C_6-C_{10} aryl, halo C_1-C_4 alkyl, an optionally substituted C_6-C_{10} aryl C_1-C_4 alkyl, an optionally substituted C_2-C_{10} heterocyclyl, an optionally substituted

C₂-C₁₀heterocyclylC₁-C₄alkyl, an optionally substituted C₁-C₁₀heteroaryl, or an optionally substituted C₁-C₁₀heteroarylC₁-C₄alkyl;

R² is C₃-C₇alkyl, haloC₁-C₄alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₇alkoxy, hydroxy, hydroxyC₁-C₄alkyl, C₁-C₆alkoxyC₁-C₄alkyl, an optionally substituted C₃-C₇cycloalkyl, an optionally substituted C₈-C₁₀aryl, an optionally substituted C₂-C₁₀heterocyclyl, or an optionally substituted C₁-C₁₀heteroaryl, provided that V-R² is not quinolin-4-ylmethyl when R¹ is an alkyl;

R³ is hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, hydroxyC₁-C₄alkyl, C₁-C₆alkoxyC₁-C₄alkyl, C₃-C₇cycloalkyl, C₃-C₇cycloalkylC₁-C₄alkyl, C₂-C₁₀heterocyclyl, C₆-C₁₀aryl, C₆-C₁₀arylC₁-C₄alkyl, C₁-C₁₀heteroaryl, halo, haloC₁-C₄alkyl, trifluoromethoxy, cyano, hydroxy, or -N(R⁸)₂;

R⁵ and R^{5a} are independently selected from hydrogen, C₁-C₆alkyl, haloC₁-C₄alkyl, hydroxy, hydroxyC₁-C₄alkyl, C₁-C₆alkoxy, C₃-C₇cycloalkylC₁-C₄alkyl and C₆-C₁₀arylC₁-C₄alkyl;

or R⁵ and R^{5a} are together to form an oxo (=O) group, or to form a C₃-C₇cycloalkyl;

R⁶, for each occurrence, is independently selected from C₁-C₆alkyl, C₆-C₁₀aryl, C₃-C₇cycloalkyl, C₁-C₁₀heteroaryl, C₂-C₁₀heterocyclyl, hydroxyC₁-C₄alkyl, haloC₁-C₄alkyl, C₁-C₆alkoxy,

C₃-C₇cycloalkylC₁-C₄alkyl, C₆-C₁₀arylC₁-C₄alkyl-N(R⁸)C(O)R¹², -C(O)N(R⁸)R¹², -OC(O)N(R⁸)R¹², -N(R⁸)C(O)OR¹², -N(R⁸)C(O)N(R⁸)R¹², -OR¹², -SR¹², -N(R⁸)R¹², -S(O)₁R¹², -N(R⁸)S(O)₂R¹², -S(O)₂N(R⁸)R¹², -OS(O)₂N(R⁸)R¹², -C(O)R¹², -OC(O)R¹², -N(R⁸)C(=N(R^{8a}))N(R⁸)R¹², -N(R⁸)C(=S)N(R⁸)R¹², -N(R⁸)((R^{8a})N=)CR¹², and -C(=N(R^{8a}))N(R⁸)R¹²;

or R⁵ and R⁸ on adjacent carbons together to form a C₃-C₇cycloalkyl or C₆-C₁₀aryl;

R⁷ is hydrogen, C₁-C₇alkyl, haloC₁-C₄alkyl, C₆-C₁₀aryl, C₃-C₇cycloalkyl, C₁-C₁₀heteroaryl, C₂-C₁₀heterocyclyl, hydroxyC₁-C₄alkyl, C₃-C₇cycloalkylC₁-C₄alkyl or aralkyl;

R⁸, for each occurrence, is independently selected from hydrogen, C₁-C₇alkyl, hydroxyC₁-C₄alkyl, C₃-C₇cycloalkyl, C₃-C₇cycloalkylC₁-C₄alkyl, C₆-C₁₀aryl, C₁-C₁₀heteroaryl, C₂-C₁₀heterocyclyl and aralkyl; and

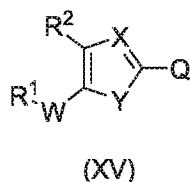
R^{8a}, for each occurrence, is independently selected from hydrogen, C₁-C₇alkyl, C₃-C₇cycloalkyl, C₃-C₇cycloalkylC₁-C₄alkyl, and cyano;

R¹², for each occurrence, is independently selected from hydrogen, C₃-C₇alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₇alkoxy, hydroxy, hydroxyC₁-C₄alkyl, C₁-C₆alkoxyC₁-C₄alkyl, C₃-C₇cycloalkyl, C₃-C₇cycloalkylC₁-C₄alkyl, C₆-C₁₀aryl, haloC₁-C₄alkyl, aralkyl, aralkyloxy, C₂-C₁₀heterocyclyl, C₂-C₁₀heterocyclylC₁-C₄alkyl, C₁-C₁₀heteroaryl, and C₁-C₁₀heteroarylC₁-C₄alkyl;

or a pharmaceutically acceptable salt thereof.

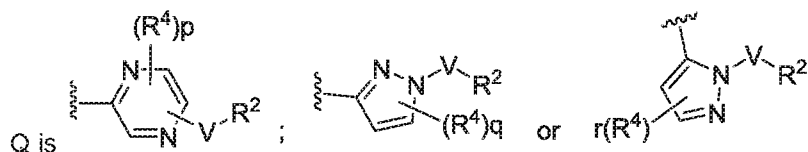
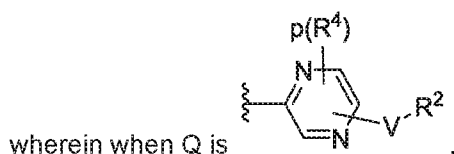
Compounds of Formula (XIV) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2011/039358. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2011/039358, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XV,



X is N or CH;

Y is NH, O, S or N-CH₃;



5 W is selected from -N(R⁶)C(O)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -N(R⁶)C(O)O-, -N(R⁶)C(O)N(R⁶)-, -O-, -N(R⁶)-, -S-, -S(O)_t-, -N(R⁶)S(O)_t-, -S(O)_tN(R⁶)-, -OS(O)_tN(R⁶)-, -C(O)-, -O(C)O-, -C(O)O-, -N(R⁶)C(=N(R^{6a}))N(R⁶)-, -N(R⁶)((R^{6a})N=C)-, -C(=N(R^{6a}))N(R⁶)-, an aryl, a heteroaryl, a heterocyclyl, an alkynylene, an alkenylene, alkylene or a direct bond;

10 V is selected from -N(R⁵)C(O)-, -C(O)N(R⁵)-, -OC(O)N(R⁵)-, -N(R⁵)C(O)O-, -N(R⁵)C(O)N(R⁵)-, -O-, -N(R⁵)-, -S-, -S(O)_t-, -N(R⁵)S(O)₂-, -S(O)₂N(R⁵)-, -OS(O)₂N(R⁵)-, -C(O)-, -O(C)O-, -C(O)O-, -CR⁵C(O)N(R⁵)-, -(CR⁵)_nC(O)-, -(CR⁵)_nO-, -(CR⁵)_nN(R⁶)-, -(CR⁵)_nN(R⁵)C(O)-, -(CR⁵)_nN(R⁵)C(O)O-, -(CR⁵)_nN(R⁵)S(O)_t-, -N(R⁵)C(=N(R^{5a}))NR⁵-, -N(R⁵)((R^{5a})N=C)-, -C(=N(R^{5a}))N(R⁵)-, -(CR⁵)_nCR⁵=CR⁵, an alkynylene, an alkenylene, an alkynyl, and alkylene or a direct bond;

t is 1 or 2;

15 p is 0, 1 or 2;

n is an integer from 1 to 6;

R¹ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl and heteroarylalkyl;

20 or R¹ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

25 R² is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl and heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

30 R³ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, trifluoromethyl, trifluoromethoxy, cyano and -N(R⁶)₂;

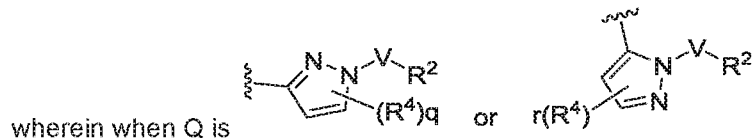
R⁴ is selected from the group consisting of alkyl, halo, -N(R⁶)₂, haloalkyl, hydroxyl, alkoxy, -N(R²)₂, cycloalkylalkyl and aralkyl;

35 R⁵ and R⁶ are independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl, cycloalkyl, hydroxyalkyl, cycloalkylalkyl and aralkyl;

R^{5a} and R^{6a} are independently selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl and cyano.

or as a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

5 In some embodiments of the compound of Formula XVa:



V is selected from $-C(O)N(R^5)-$, $-S(O)_t-$, $-S(O)_2N(R^5)-$, $-C(O)-$, $-C(C)O-$, $-CR^{5_2}C(O)N(R^5)-$, $-(CR^{5_2})_nC(O)-$, $-(CR^{5_2})_nO-$, $-(CR^{5_2})_nN(R^6)-$, $-(CR^{5_2})_nN(R^5)C(O)-$, $-(CR^{5_2})_nN(R^5)C(O)O-$, $-(CR^{5_2})_nN(R^5)S(O)_t-$, an aryl, a heteroaryl, a heterocyclyl, an alkynylene, an alkenylene, an alkylene or a direct bond;

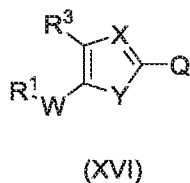
10 r is 0, 1 or 2;

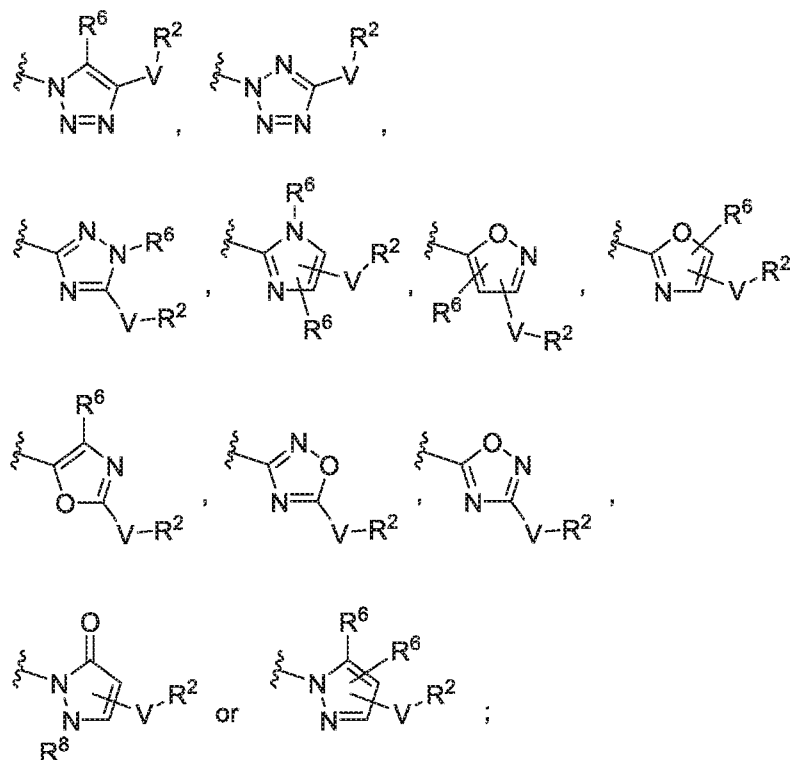
R^4 is selected from the group consisting of alkyl, haloalkyl, hydroxyl, alkoxy, $-N(R^2)_2$, cycloalkylalkyl and aralkyl;

R^{5a} and R^{6a} are independently selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl and cyano.

15 Compounds of Formula (XV) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/024390. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/024390, the compounds of which are herein incorporated by reference.

20 In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XVI,





wherein when Q is

W is -N(R⁷)C(O)-, -C(O)N(R⁷)-, -OC(O)N(R⁷)-, -N(R⁷)C(O)O-, -N(R⁷)C(O)N(R⁷)-, -N(R⁷)-, -O-, -S-, -S(O)-, -N(R⁷)S(O)-, -S(O)N(R⁷)-, -OS(O)N(R⁷)-, -C(O)-, -O(C)O-, -C(O)O-, -N(R⁷)C(=N(R^{7a}))N(R⁷)-, -N(R⁷)C(=S)N(R⁷)-, -N(R⁷)((R^{7a})N)=C-, -C(=N(R^{7a}))N(R⁷)-, an alkenylene group, an alkynylene group or a direct bond;

V is -N(R⁷)C(O)-, -N(R⁷)C(O)O-, -N(R⁷)C(O)N(R⁷)-, -N(R⁷)-, -N(R⁷)S(O)₂-, -O-, -S-, -S(O)_t, -N(R⁷)S(O)_t, -S(O)₂N(R⁷)-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R⁷)-, -OC(O)N(R⁷)-, -C(R⁷)_nC(O)N(R⁷)-, -(CR⁷)_nC(O)-, -(CR⁷)_nO-, -(CR⁷)_n-, -(CR⁷)_nN(R⁷)-, -(CR⁷)_nN(R⁷)C(O)-, -(CR⁷)_nN(R⁷)C(O)N(R⁷)-, -C(=N(R^{7a}))N(R⁷)-, an alkenylene group, an alkynylene group or a direct bond;

X is N or CH:

Y is NH, O, S or N-CH₃;

t is 1 or 2;

n is an integer from 1 to 6;

R¹ is selected from the group consisting of hydrogen, alkyl, alkenyl, hydroxyalkyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R¹ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R² is selected from the group consisting of hydrogen, alkyl, alkenyl, hydroxyalkyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is selected from the group consisting of hydrogen, alkyl, alkenyl, hydroxyalkyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, trifluoromethyl, trifluoromethoxyl, cyano, nitro and $-N(R^7)_2$;

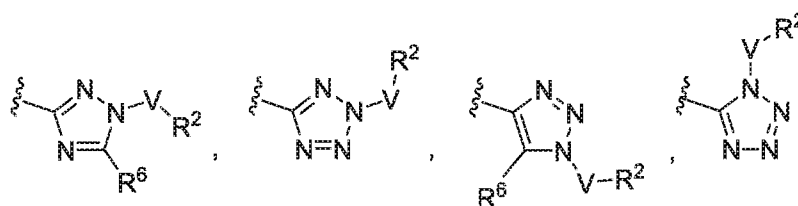
R^6 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl and aralkyl; each R^7 is the same or different and independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkenyl, alkynyl, aryl, alkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl and aralkyl;

R^{7a} is selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl and cyano; and

R^8 is hydrogen or alkyl; or

a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

or



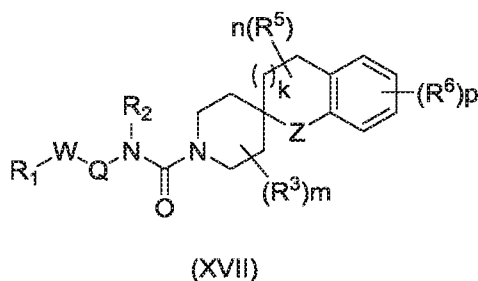
wherein when Q is

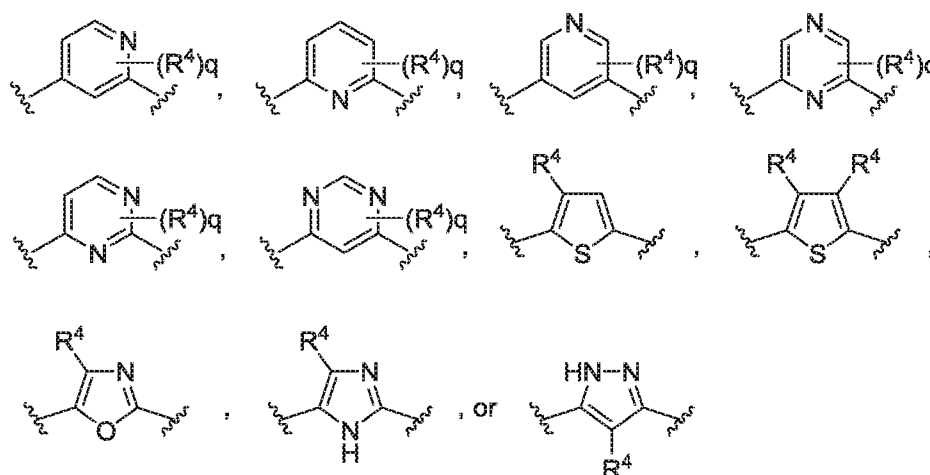
W is $-N(R^7)C(O)-$, $-C(O)N(R^7)-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)O-$, $-N(R^7)C(O)N(R^7)-$, $-O-$, $-S-$, $-S(O)_t-$, $-N(R^7)S(O)_t-$, $-S(O)_tN(R^7)-$, $-OS(O)_tN(R^7)-$, $-C(O)-$, $-O(C)O-$, $-C(O)O-$, $-N(R^7)C(=N(R^{7a}))N(R^7)-$, $-N(R^7)C(=S)N(R^7)-$, $-N(R^7)((R^{7a})N=C)-$, $-C(=N(R^{7a}))N(R^7)-$, an alkenylene group, an alkynylene group or a direct bond;

V is $-S(O)_t-$, $-S(O)_2N(R^7)-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^7)-$, $-C(R^{7_2})_nC(O)N(R^7)-$, $-(CR^{7_2})_nC(O)-$, $-(CR^{7_2})_nO-$, $-(CR^{7_2})_n-$, $-(CR^{7_2})_nN(R^7)-$, $-(CR^{7_2})_nN(R^7)C(O)-$, $-(CR^{7_2})_nN(R^7)C(O)N(R^7)-$, $-C(=N(R^{7a}))N(R^7)-$, an alkenylene group, an alkynylene group or a direct bond.

Compounds of Formula (XVI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/074835. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/074835, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XVII,





wherein Q is

W is $-N(R^7)C(O)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)N(R^7)-$, $-N(R^7)S(O)-$, $-S(O)N(R^7)-$, or a direct bond;

Z is $-C(R^4)-$, $-C(O)-$, $-O-$, $-N(R^7)-$, $-S(O)-$, $-O-$ or $-S-$;

k is 0 or 1;

5 m is 0 to 8;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 1, 2, or 3;

t is 1 or 2;

10 u is 1 or 2;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

or R^1 is a multi-ring structure having 2 to 4 rings wherein the rings are independently cycloalkyl, heterocyclyl, aryl or heteroaryl and where some or all of the rings may be fused to each other;

15 R^2 is hydrogen, or alkyl;

R^3 is independently alkyl, halo, haloalkyl, hydroxy, or $-N(R^7)_2$;

R^4 is independently alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, haloalkoxy, cyano, hydroxy or $-N(R^7)_2$;

20 R^5 is independently alkyl, halo, haloalkyl, hydroxy, cycloalkyl or $-N(R^7)_2$;

or two R^5 's on the same carbon atom form an oxo ($=O$);

R^6 is independently alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, haloalkoxy, cyano, hydroxy or $-N(R^7)_2$; and

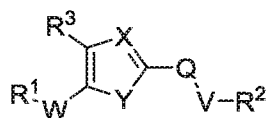
25 R^7 is independently hydrogen, alkyl, alkenyl, hydroxyalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl; or

a pharmaceutically acceptable salt thereof or a prodrug thereof.

Compounds of Formula (XVII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2010/112520. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2010/112520, the compounds of which are herein incorporated by reference.

30

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XVIII,

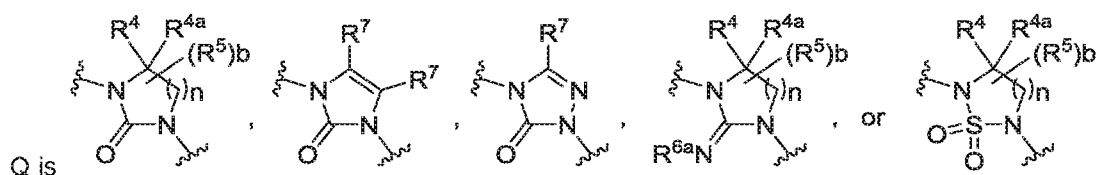


(XVIII)

wherein:

X is Nor CH:

Y is NH, O, S or N-CH₃;



W is selected from -N(R⁶)C(O)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -N(R⁶)C(O)O-, -N(R⁶)C(O)N(R⁶)-, -O-, -S-, -N(R⁶)-, -S(O)-, -N(R⁶)S(O)-, -S(O)N(R⁶)-, -OS(O)N(R⁶)-, -C(O)-, -O(C)O-, -C(O)O-, -N(R⁶)C(=N(R^{6a}))N(R⁶)-, -N(R⁶)((R^{6a})N=C)-, -C(=N(R^{6a}))N(R⁶)-, or a direct bond;

V is selected from -R⁸-C(O)N(R⁶)-, -R⁸-OC(O)N(R⁶)-, -S(O)-, -S(O)₂N(R⁶)-, -R⁸-C(O)-, -R⁸-O(C)O-, -C(=N(R^{6a}))N(R⁶)-, or a direct bond;

n is 1, 2, or 3;

p is 0, 1, 2, to 2n;

t is 1 or 2;

R¹ is selected from the group consisting of halo, hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

or R¹ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R² is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, haloalkoxy, cyano, or -N(R⁶)₂;

each of R⁴ and R^{4a} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, cycloalkylalkyl or aralkyl;

or R⁴ and R^{4a} are together to form an oxo (=O) group or a cycloalkyl;

R^5 is selected from the group consisting of alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, alkoxy, cycloalkylalkyl, aralkyl, $-N(R^6)C(O)R^2$ -, $-C(O)N(R^6)R^2$ -, $-OC(O)N(R^6)R^2$ -, $-N(R^6)C(O)OR^2$ -, $-N(R^6)C(O)N(R^6)R^2$ -, $-OR^2$ -, $-SR^2$ -, $-N(R^6)R^2$ -, $-S(O)_tR^2$ -, $-N(R^6)S(O)_2R^2$ -, $-S(O)_2N(R^6)R^2$ -, $-OS(O)_2N(R^6)R^2$ -, $-C(O)R^2$ -, $-O(C)OR^2$ -, $-C(O)OR^2$ -, $-N(R^6)C(=N(R^{6a}))N(R^6)R^2$ -,

5 $-N(R^6)C(=S)N(R^6)R^2$ -, $-N(R^6)((R^{6a}))N(=)CR^2$ -, or $-C(=N(R^{6a}))N(R^6)R^2$;

each R^6 is independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl or aralkyl;

each R^{6a} is independently selected from the group consisting of hydrogen, alkyl, cycloalkylalkyl, or cyano;

10 each R^7 is independently selected from the group consisting of hydrogen, alkyl, trifluoromethyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, cycloalkylalkyl or aralkyl; and

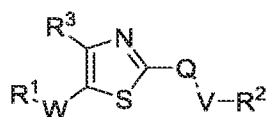
each R^8 is independently a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; or

15 as a stereoisomer, enantiomer or tautomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prod rug thereof.

Compounds of Formula (XVIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/127349. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/127349, the

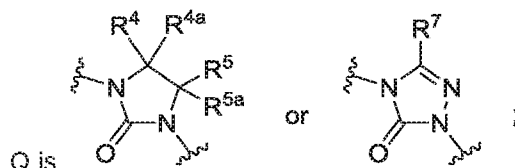
20 compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XIX,



(XIX)

wherein:



25 Q is $-N(R^6)C(O)$ -, $-R^8-C(O)N(R^6)$ -, $-R^8-OC(O)N(R^6)$ -, $-N(R^6)C(O)O$ -, $-N(R^6)C(O)N(R^6)$ -, $-O$ -, $-S$ -, $-N(R^6)$ -, $-S(O)_t$ -, $-N(R^6)S(O)_t$ -, $-S(O)_tN(R^6)$ -, $-OS(O)_tN(R^6)$ -, $-R^8-C(O)$ -, $-O(C)O$ -, $-C(O)O$ -, $-N(R^6)C(=N(R^{6a}))N(R^6)$ -, $-N(R^6)((R^{6a}))N(=)C$ -, $-C(=N(R^{6a}))N(R^6)$ -, or a direct bond;

V is selected from $-C(O)N(R^6)$ -, $-S(O)_t$ -, $-S(O)_2N(R^6)$ -, $-C(O)$ -, $-R^8-C(O)O$ -, $R^8-OC(O)N(R^6)$ -,

30 $R^8-C(O)N(R^6)$ -, $-R^8-C(O)$ -, $-C(=N(R^{6a}))N(R^6)$ -, or a direct bond;

t is 1 or 2;

R^1 is halo, hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

or R¹ is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R² is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl;

or R² is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R³ is hydrogen or alkyl;

R⁴ and R^{4a} are independently hydrogen, alkyl, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, cycloalkylalkyl or aralkyl;

or R⁴ and R^{4a} are taken together to form an oxo (=O) group, cycloalkyl or heterocyclyl;

R⁵ and R^{5a} are independently hydrogen, alkyl or haloalkyl;

R⁴ and R⁵ are taken from a cycloalkyl, aryl, heteroaryl or heterocyclyl, and the remaining R^{4a} and R^{5a} are as described above;

R⁶ is independently hydrogen, alkyl, hydroxyalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl or aralkyl;

R^{6a} are independently hydrogen, alkyl cycloalkylalkyl, or cyano;

R⁷ is hydrogen, alkyl, trifluoromethyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, cycloalkylalkyl or aralkyl; and

R⁸ is independently a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; or

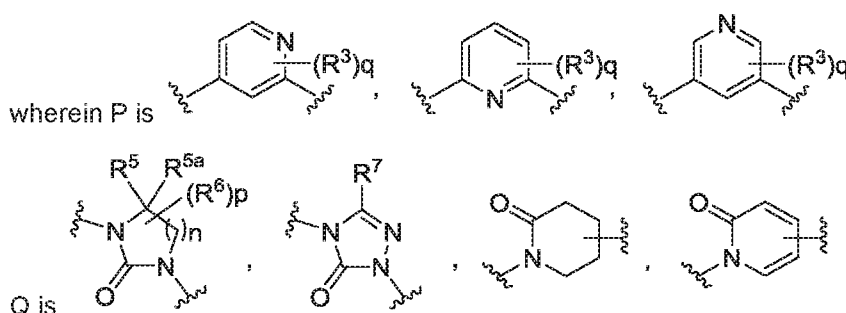
as a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or as a prodrug thereof.

Compounds of Formula (XIX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/103739. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/103739, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XX,



(XX)



W is selected from $-N(R^6)C(O)-$, $-C(O)N(R^6)-$ or a direct bond;

n is 1, 2, or 3;

p is 0, 1, 2, to $2n$;

q is 0, 1, 2, or 3;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

R^2 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, haloalkyl, aralkyl, aralkyloxy, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl;

R^3 is alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, halo, haloalkyl, trifluoromethoxyl, cyano, hydroxy, or $-N(R^6)_2$;

R^5 and R^{5a} are independently hydrogen, alkyl, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, cycloalkylalkyl or aralkyl;

or R^5 and R^{5a} are together to form an oxo ($=O$) group, or to form a cycloalkyl;

R^6 is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, haloalkyl, alkoxy, cycloalkylalkyl, or aralkyl;

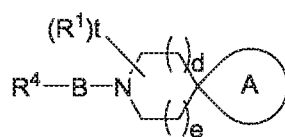
or R^5 and R^6 on adjacent carbons are together to form a cycloalkyl, or to form an aryl;

R^7 is hydrogen, alkyl, haloalkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, hydroxyalkyl, cycloalkylalkyl or aralkyl; and

R^8 is hydrogen, alkyl, hydroxyalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, or aralkyl; or a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

Compounds of Formula (XX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/156484. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/156484, the compounds of which are herein incorporated by reference.

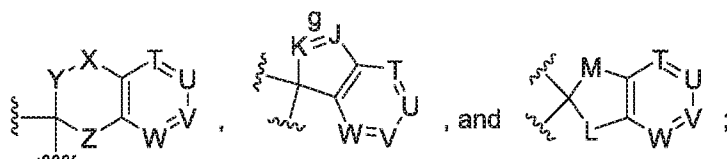
In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXI,



(XXIa, XXIb)

or a pharmaceutically acceptable salt thereof; wherein

A is selected from the group consisting of:



g is a single bond or a double bond;

J and K are each independently selected from the group consisting of: S, O, NH, CH and CH₂, wherein each NH is unsubstituted or substituted with R^g, and wherein each CH and CH₂ is unsubstituted or substituted with R₂, provided that when g is a single bond at least one of J and K is CH₂ unsubstituted or substituted with R₂, and further provided that when g is a double bond then both J and K are CH;

5 L and M are each independently selected from the group consisting of: S, O, NH and CH₂, wherein each NH is unsubstituted or substituted with R^g, and wherein each CH₂ is unsubstituted or substituted with R²;

T, U, V and W are each independently selected from N and CH, wherein each CH is unsubstituted or substituted with R³, provided that at least two of T, U, V and W are CH;

10 X is CH₂, wherein CH₂ is unsubstituted or substituted with R²;

Y is independently selected from the group consisting of: O, NH and CH₂, wherein each NH is unsubstituted or substituted with R^g, and wherein each CH₂ is unsubstituted or substituted with R²;

Z is independently selected from the group consisting of: S, S(O), S(O)₂, O, NH and CH₂, wherein each NH is unsubstituted or substituted with R^g, and wherein each CH₂ is unsubstituted or substituted
15 with R²;

each R¹ is independently selected from the group consisting of: hydrogen, halogen, and C₁₋₃alkyl, wherein alkyl is unsubstituted or substituted with one to three substituents independently selected from halogen and hydroxy;

each R² is independently selected from the group consisting of: hydrogen, halogen, oxo, C₁₋₆alkyl, (CH₂)_nOR^e, (CH₂)_nN(R^e)₂, (CH₂)_nC≡N, (CH₂)_nCOR^e, and (CH₂)_nS(O)_qR^e,
20

wherein alkyl is unsubstituted or substituted with hydroxy or one to three halogens, and wherein any CH₂ in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

each R^a is independently selected from the group consisting of:

25 hydrogen,

halogen,

cyano,

C₁₋₄alkyl, unsubstituted or substituted with one to five fluorines,

C₁₋₄alkoxy, unsubstituted or substituted with one to five fluorines,

30 C₁₋₄alkylthio, unsubstituted or substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,

-CO₂H,

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

35 each R^b is independently selected from the group consisting of: hydrogen, and C₁₋₄alkyl, wherein alkyl is unsubstituted or substituted with one to five fluorines;

each R^c is independently selected from the group consisting of: -(CH₂)_mCO₂H, -(CH₂)_mCO₂C₁₋₃alkyl, -(CH₂)_m-NR^b-(CH₂)_pCO₂H, -(CH₂)_m-NR^b-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_m-O-(CH₂)_pCO₂H,

-(CH₂)_m-O-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_m-S-(CH₂)_pCO₂H, and -(CH₂)_m-S-(CH₂)_pCO₂C₁₋₃alkyl,

wherein any CH₂ in R^c is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

each R^d is independently selected from the group consisting of: -(CH₂)_nCO₂H,

5 -(CH₂)_nCO₂C₁₋₃alkyl, -(CH₂)_nNR^b-(CH₂)_pCO₂H, -(CH₂)_nNR^b-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_n-O-(CH₂)_pCO₂H, -(CH₂)_n-O-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_n-S-(CH₂)_pCO₂H, and -(CH₂)_n-S-(CH₂)_pCO₂C₁₋₃alkyl,

wherein any CH₂ in R^d is unsubstituted or substituted with one to two groups independently selected from the group consisting of: halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

10 each R^e is independently selected from the group consisting of: hydrogen, and C₁₋₆alkyl,

wherein alkyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of: halogen, cyano, -C₁₋₄alkoxy, -C₁₋₄alkylthio, -C₁₋₄alkylsulfonyl, -CO₂H, and -CO₂C₁₋₄alkyl;

each R^g is independently selected from the group consisting of: hydrogen, and C₁₋₆alkyl,

15 m is an integer from 1 to 3;

n is an integer from 0 to 3;

p is an integer from 1 to 3;

q is an integer from 1 to 2;

t is an integer from 0 to 8;

20 d is an integer from 0 to 2; and

e is an integer from 0 to 2,

provided that d + e is 2.

In some embodiments of the compound of Formula XXIIa,

B is a 5 membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from NH, O and S,

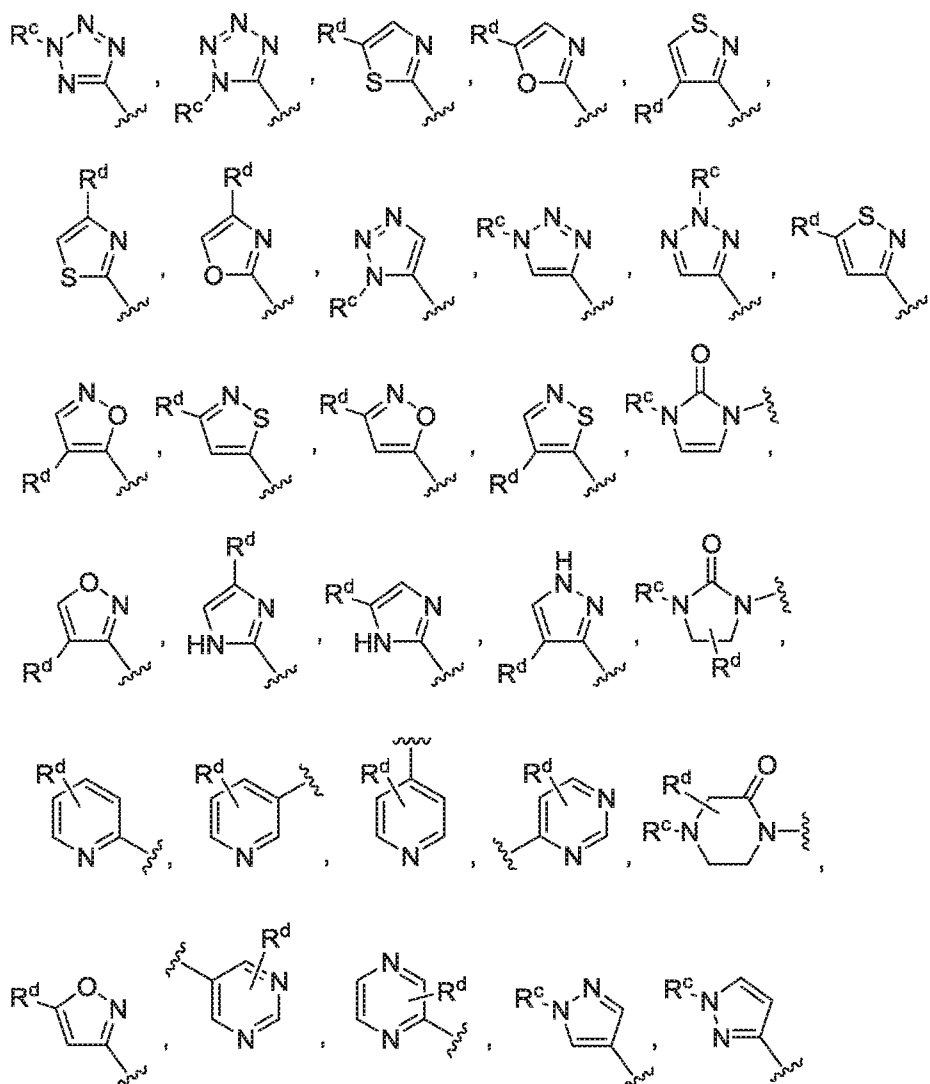
25 wherein any CH is unsubstituted or substituted with one substituent selected from R^a, and wherein any NH is unsubstituted or substituted with one substituent selected from R^b;

each R³ is independently selected from the group consisting of: hydrogen, halogen, -C₁₋₆alkyl, -C₁₋₆alkenyl, -OC₁₋₆alkyl, (CH₂)_nOR^e, (CH₂)_nN(R^e)₂, (CH₂)_nC≡N, (CH₂)_nCOR^e, and (CH₂)_nS(O)_qR^e,

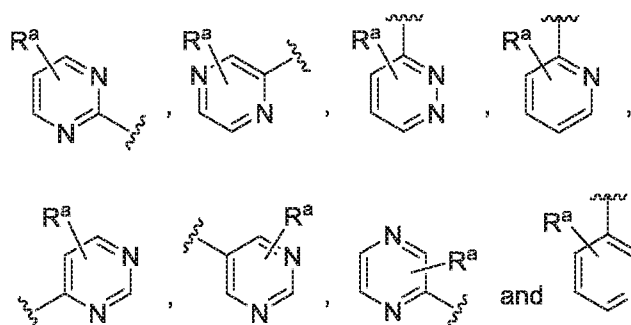
30 wherein alkyl is unsubstituted or substituted with one to three substituents selected from: hydroxy, halogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₂₋₅cycloheteroalkyl, aryl, and heteroaryl,

wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with one to three substituents selected from: halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines, and wherein any CH₂ in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

R⁴ is selected from the group consisting of:



In some embodiments of the compound of Formula XXIb, B is selected from the group consisting of:



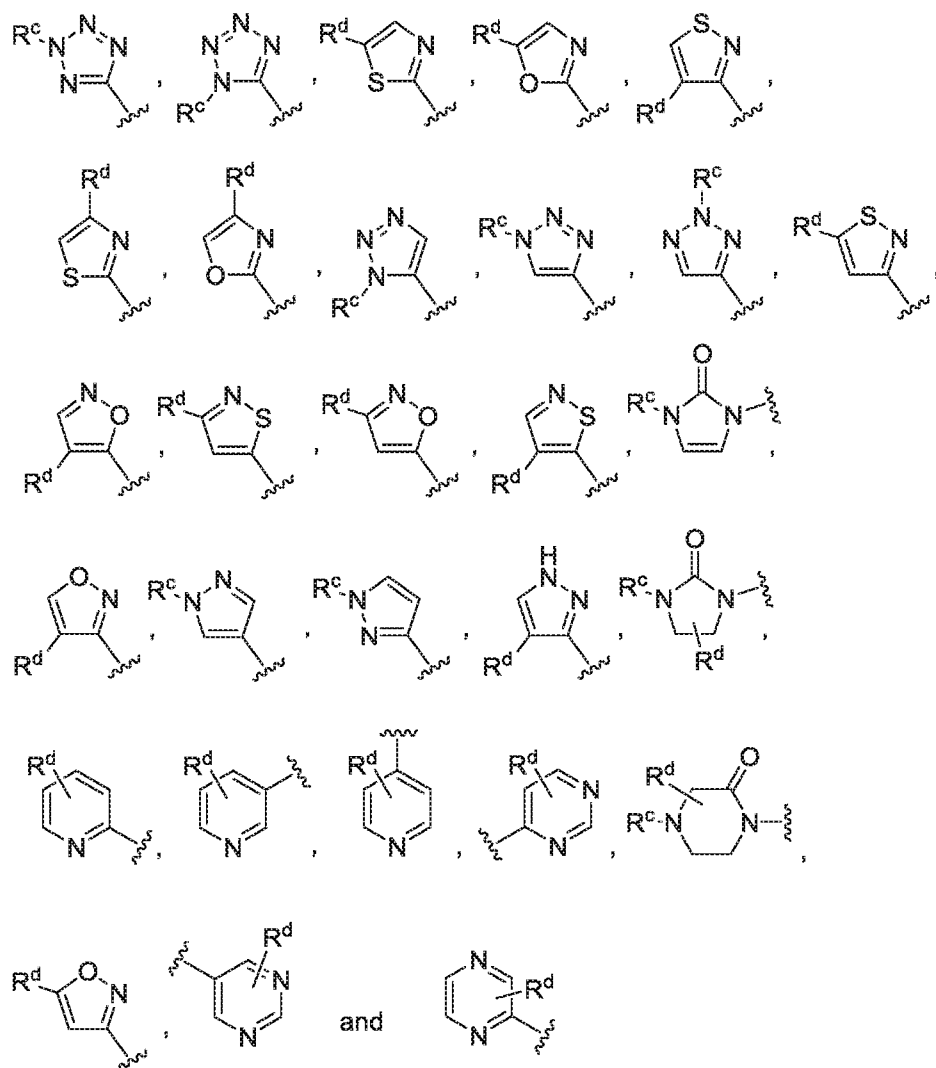
5

each R^3 is independently selected from the group consisting of: hydrogen, halogen, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $(CH_2)_nOR^e$, $(CH_2)_nN(R^e)_2$, $(CH_2)_nC\equiv N$, $(CH_2)_nCOR^e$, and $(CH_2)_nS(O)_qR^e$,

wherein alkyl is unsubstituted or substituted with hydroxy or one to three halogens, and wherein any CH_2 in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;

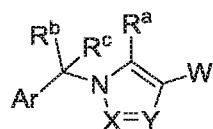
10

R^4 is selected from the group consisting of:



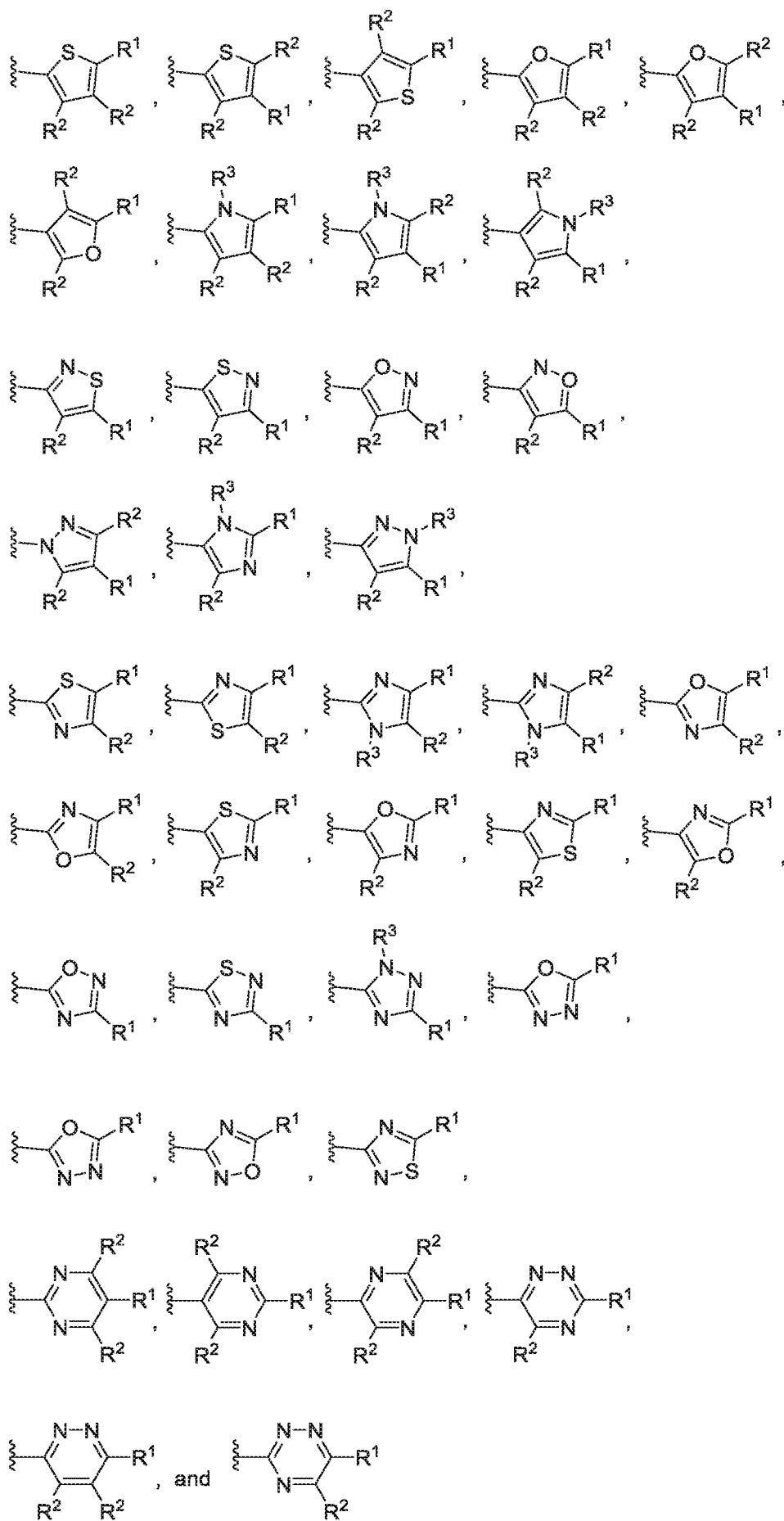
Compounds of Formula (XXI) may be synthesized by methods known in the art, e.g., those described in International Patent Publications No. WO2010/094120 and WO2011/047481. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publications No. WO2010/094120 and WO2011/047481, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXII,

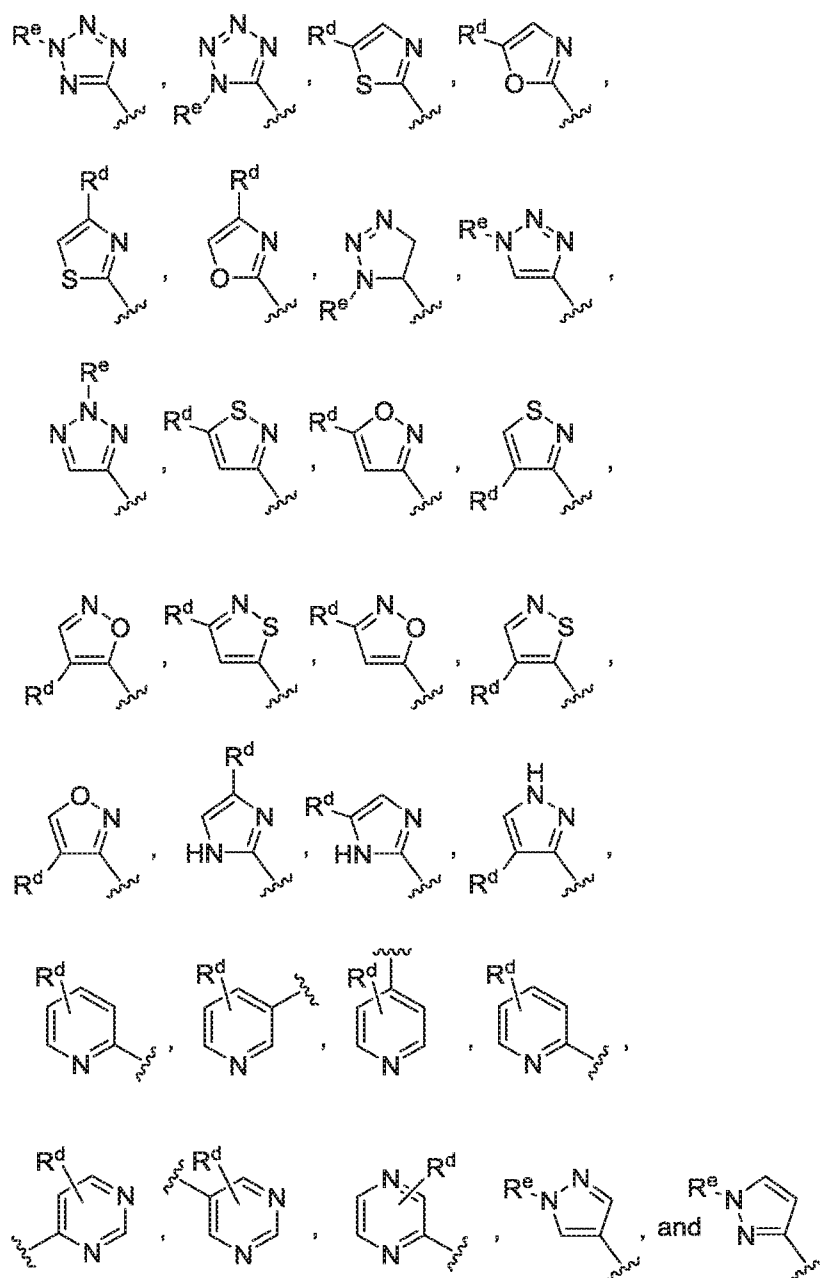


(XXI)

or a pharmaceutically acceptable salt thereof;
wherein X and Y are each independently CH or N;
W is heteroaryl selected from the group consisting of:



R¹ is heteroaryl selected from the group consisting of:



wherein

5 R^d is -(CH₂)_nCO₂H, -(CH₂)_nCO₂C₁₋₃alkyl, -(CH₂)_n-Z-(CH₂)_pCO₂H, or -(CH₂)_n-Z-(CH₂)_pCO₂C₁₋₃alkyl;

R^e is -(CH₂)_mCO₂H, -(CH₂)_mCO₂C₁₋₃alkyl, -(CH₂)_m-Z-(CH₂)_pCO₂H, or

-(CH₂)_m-Z-(CH₂)_pCO₂C₁₋₃alkyl;

m is an integer from 1 to 3;

p is an integer from 1 to 3;

10 n is an integer from 0 to 3;

Z is O or S;

each R² is independently selected from the group consisting of:

hydrogen,

halogen,

15 cyano,

C₁₋₄alkyl, optionally substituted with one to five fluorines,
 C₁₋₄alkoxy, optionally substituted with one to five fluorines,
 C₁₋₄alkylthio, optionally substituted with one to five fluorines,
 C₁₋₄alkylsulfonyl,
 5 carboxy,
 C₁₋₄alkyloxycarbonyl, and
 C₁₋₄alkylcarbonyl;
 R³ is hydrogen or C₁₋₄ alkyl wherein alkyl is optionally substituted with one to five fluorines;
 Ar is phenyl or pyridyl each of which is optionally substituted with one to five substituents

10 independently selected from the group consisting of:

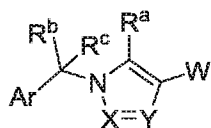
halogen,
 C₁₋₆alkyl optionally substituted with one to five fluorines,
 C₂₋₆alkenyl,
 C₂₋₆alkynyl,
 15 C₁₋₆alkylthio, optionally substituted with one to five fluorines,
 C₁₋₆alkoxy, optionally substituted with one to five fluorines, and
 C₃₋₆cycloalkyl;
 R^a is hydrogen or C₁₋₄ alkyl wherein alkyl is optionally substituted with one to five fluorines; and
 R^b and R^c are each independently hydrogen, fluorine, or C₁₋₄ alkyl wherein alkyl is optionally

20 substituted with one to five fluorines;

or R^b and R^c are taken together to form a 3- to 6-membered saturated carbocyclic ring optionally containing a heteroatom selected from the group consisting of O, S, and N.

Compounds of Formula (XXII) may be synthesized by methods known in the art, e.g., those
 described in International Patent Publication No. WO2010/025553. In some embodiments, the SCD
 25 inhibitor is a compound disclosed in International Patent Publication No. WO2010/025553, the
 compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXIII,

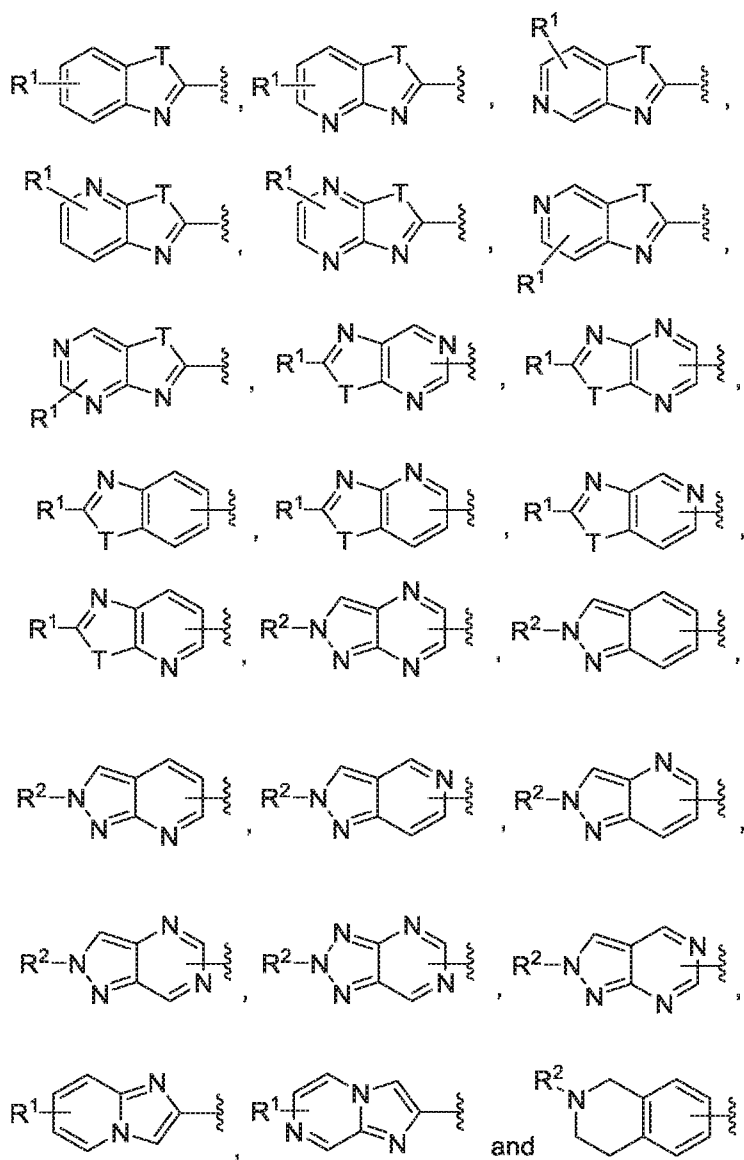


(XXIII)

30 or a pharmaceutically acceptable salt thereof; wherein

X and Y are each independently CH or N;

W is heteroaryl selected from the group consisting of:



wherein W is further optionally substituted with one to two substituents independently selected

R¹ is selected from the group consisting of: $-(CH_2)_pCO_2H$, $-(CH_2)_pCO_2C_{1-4}alkyl$, $-Z(CH_2)_mCO_2H$, $-Z(CH_2)_mCO_2C_{1-4}alkyl$, $-(CH_2)_nOR^5$, $-(CH_2)_n-CONR^6R^7$, $-(CH_2)_n-ONR^6R^7$, $-(CH_2)_n-SO_2NR^6R^7$, $-(CH_2)_n-SO_2R^8$, $-(CH_2)_n-NR^9SO_2R^8$, $-(CH_2)_n-NR^9CONR^6R^7$, $-(CH_2)_n-NR^9COR^9$, and $-(CH_2)_n-NR^9CO_2R^8$;

R^2 is $-(CH_2)_mCO_2H$ or $-(CH_2)_mCO_2C_{1-3}alkyl$;

each m is independently an integer from 1 to 3;

each n is independently an integer from 0 to 3;

each p is independently an integer from 0 to 3;

T is O, S, or NR⁵:

Z is O, S, or NR⁵;

each R^4 is independently selected from the group consisting of:

hydrogen,

halogen,

cyano,

C₁₋₄alkyl, optionally substituted with one to five fluorines,

C₁₋₄alkoxy, optionally substituted with one to five fluorines,

C₁₋₄alkylthio, optionally substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,

carboxy,

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

R⁵ is hydrogen or C₁₋₄alkyl wherein alkyl is optionally substituted with one to five fluorines;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen,

(CH₂)_n-phenyl,

(CH₂)_n-C₃₋₆cycloalkyl, and

C₁₋₆ alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxy and wherein phenyl and cycloalkyl are optionally substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆alkyl, and C₁₋₆alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

or R⁶ and R⁷ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆alkyl, and C₁₋₆alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines;

each R⁸ is independently C₁₋₆alkyl, wherein alkyl is optionally substituted with one to five substituents independently selected from fluorine and hydroxyl;

R⁹ is hydrogen or R⁸;

Ar is phenyl or pyridyl each of which is optionally substituted with one to five substituents independently selected from the group consisting of:

halogen,

C₁₋₆alkyl optionally substituted with one to five fluorines,

C₂₋₆alkenyl,

C₂₋₆alkynyl,

C₁₋₆alkylthio, optionally substituted with one to five fluorines,

C₁₋₆alkoxy, optionally substituted with one to five fluorines, and

C₃₋₆cycloalkyl;

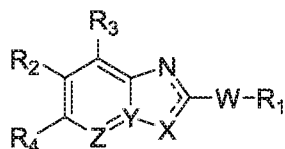
R^a is hydrogen or C₁₋₄alkyl wherein alkyl is optionally substituted with one to five fluorines; and

R^b and R^c are each independently hydrogen, fluorine, or C₁₋₄alkyl wherein alkyl is optionally substituted with one to five fluorines;

or R^b and R^c are taken together to form a 3- to 6-membered saturated carbocyclic ring optionally containing a heteroatom selected from the group consisting of O, S, and N.

Compounds of Formula (XXIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2010/037225. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2010/037225, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXIV,



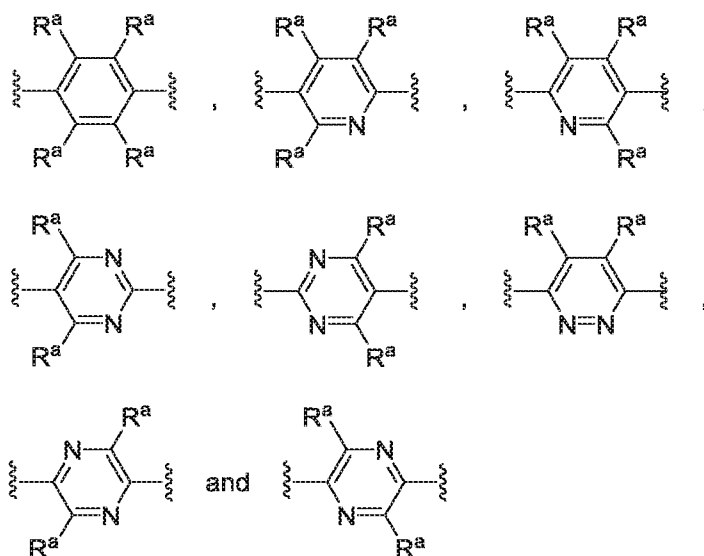
(XXIV)

or a pharmaceutically acceptable salt thereof; wherein

X is NH, Y is C, and Z is N or CR⁵;

or X and Z are each CR⁵, and Y is N;

W is a residue selected from the group consisting of:



wherein each R^a is independently selected from the group consisting of:

hydrogen,

halogen,

C₁₋₄alkyl, optionally substituted with one to five fluorines, and

C₁₋₄alkoxy, optionally substituted with one to five fluorines;

R³, R⁴, and each R⁵ are each independently selected from the group consisting of:

hydrogen,

halogen,

C₁₋₄alkyl, optionally substituted with one to five fluorines, and

C₁₋₄alkoxy, optionally substituted with one to five fluorines;

R² is selected from the group consisting of:

SO₂cyclopropyl,

SC₁₋₃alkyl, optionally substituted with one to five fluorines,

S(O)C₁₋₃alkyl, optionally substituted with one to five fluorines,

SO₂C₁₋₃alkyl, optionally substituted with one to five fluorines, and

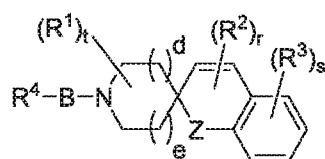
SO₂NR^bR^b, wherein each R^b is independently hydrogen or C₁₋₃alkyl; and

R¹ is selected from the group consisting of: cyclopentenyl, cyclohexenyl, phenyl, and heteroaryl selected from the group consisting of: pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, furyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, and pyrazolyl;

wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, cyano, and C₁₋₃alkyl wherein alkyl is optionally substituted with one to five fluorines.

Compounds of Formula (XXIV) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/129625. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/129625, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXV,



(XXV)

or a pharmaceutically acceptable salt thereof, wherein:

Z is independently selected from the group consisting of: S, S(O), S(O)₂, O, NH and CH₂, wherein each NH is unsubstituted or substituted with R^a, and wherein CH₂ is unsubstituted or substituted with R²;

B is a 5 membered heteroaryl ring containing 1, 2 or 3 heteroatoms selected from NH, O and S, wherein any CH is unsubstituted or substituted with one substituent selected from R^a, and wherein any NH is unsubstituted or substituted with one substituent selected from R^b;

each R¹ is independently selected from the group consisting of: hydrogen, halogen, and C₁₋₃alkyl, wherein alkyl is unsubstituted or substituted with one to three substituents independently selected from halogen and hydroxy;

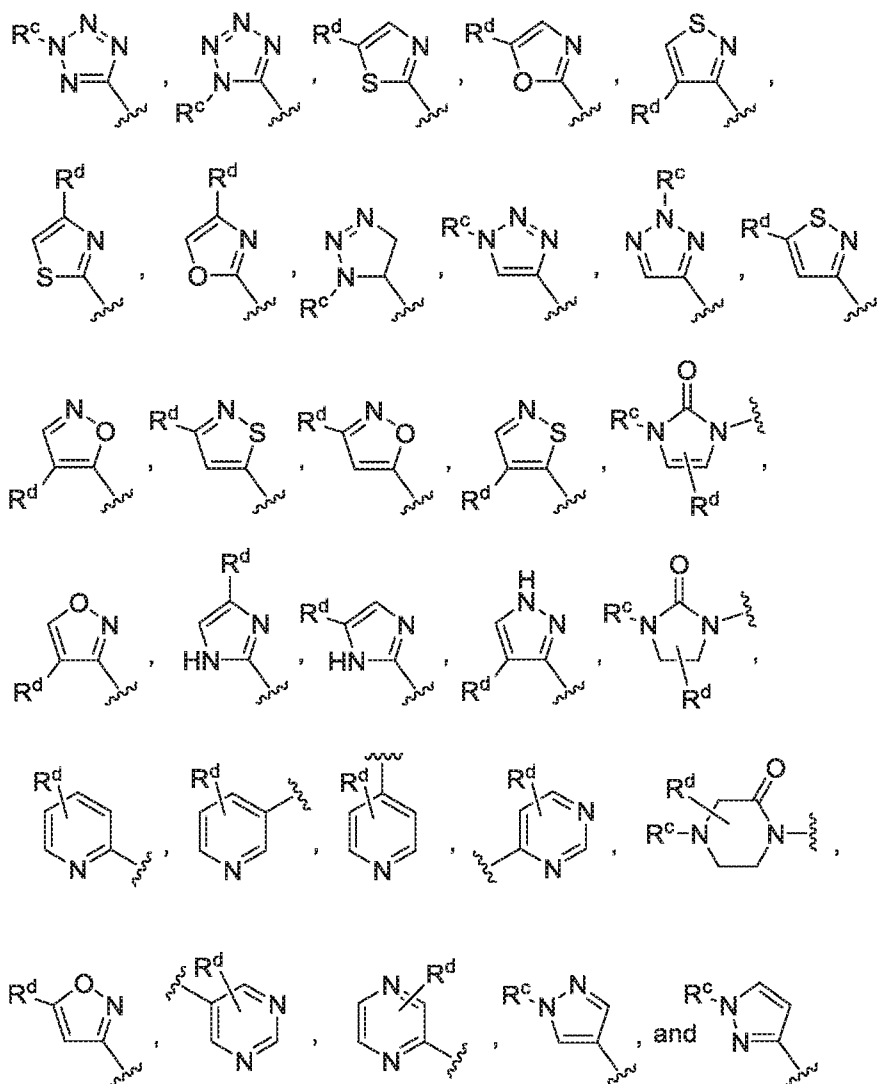
each R² is independently selected from the group consisting of: hydrogen, halogen, aryl, heteroaryl, biphenyl, C₁₋₆alkyl, (CH₂)_nOR^e, (CH₂)_nN(R^e)₂, (CH₂)_nC≡N, (CH₂)_nCOR^e, and (CH₂)_nS(O)_qR^e,

wherein CH₂, alkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from R^f;

each R³ is independently selected from the group consisting of: hydrogen, halogen, -C₁₋₆alkyl, -OC₁₋₆alkyl, (CH₂)_nOR^e, (CH₂)_nN(R^e)₂, (CH₂)_nC≡N, (CH₂)_nCOR^e, and (CH₂)_nS(O)_qR^e,

wherein alkyl is unsubstituted or substituted with hydroxy or one to three halogens, and wherein any CH₂ in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five fluorines;

R⁴ is selected from the group consisting of:



each R^a is independently selected from the group consisting of:

hydrogen,

halogen,

cyano,

C₁₋₄alkyl, unsubstituted or substituted with one to five fluorines,

C₁₋₄alkoxy, unsubstituted or substituted with one to five fluorines.

C₁₋₄alkylthio, unsubstituted or substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,

 $-\text{CO}_2\text{H},$

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

each R^b is independently selected from the group consisting of: hydrogen, and C₁₋₄alkyl,

wherein alkyl is unsubstituted or substituted with one to five fluorines;

each R^c is independently selected from the group consisting of: -(CH₂)_mCO₂H,

$$-(\text{CH}_2)_m\text{CO}_2\text{C}_{1-3}\text{alkyl}, -(\text{CH}_2)_m\text{NR}^b-(\text{CH}_2)_p\text{CO}_2\text{H}, -(\text{CH}_2)_m\text{NR}^b-(\text{CH}_2)_p\text{CO}_2\text{C}_{1-3}\text{alkyl}, -(\text{CH}_2)_m\text{O}-(\text{CH}_2)_p\text{CO}_2\text{H},$$
$$-(\text{CH}_2)_m\text{-O-(CH}_2)_p\text{CO}_2\text{C}_{1-3}\text{alkyl}, -(\text{CH}_2)_m\text{-S-(CH}_2)_p\text{CO}_2\text{H}, \text{ and } -(\text{CH}_2)_m\text{-S-(CH}_2)_p\text{CO}_2\text{C}_{1-3}\text{alkyl},$$

wherein any CH₂ in R^c is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

each R^d is independently selected from the group consisting of: -(CH₂)_nCO₂H,

-(CH₂)_nCO₂C₁₋₃alkyl, -(CH₂)_nNR^b-(CH₂)_pCO₂H, -(CH₂)_nNR^b-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_n-O-(CH₂)_pCO₂H,
5 -(CH₂)_n-O-(CH₂)_pCO₂C₁₋₃alkyl, -(CH₂)_n-S-(CH₂)_pCO₂H, and -(CH₂)_n-S-(CH₂)_pCO₂C₁₋₃alkyl,

where in any CH₂ in R^d is unsubstituted or substituted with one to two groups independently selected from the group consisting of: halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

each R^e is independently selected from the group consisting of: hydrogen, and C₁₋₆alkyl,

10 wherein alkyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of: halogen, cyano, -C₁₋₄alkoxy, -C₁₋₄alkylthio, -C₁₋₄alkylsulfonyl, -CO₂H, and -CO₂C₁₋₄alkyl;

each R^f is independently selected from the group consisting of: hydrogen, halogen, -C₁₋₆alkyl, -OC₁₋₆alkyl, (CH₂)_nOR^e, (CH₂)_nN(R^e)₂, (CH₂)_nC≡N, (CH₂)_nCOR^e, (CH₂)_nS(O)_qR^e, and aryl,

15 wherein CH₂, alkyl and aryl are unsubstituted or substituted with one, two or three groups independently selected from halogen, hydroxy, and C₁₋₄alkyl unsubstituted or substituted with one to five fluorines;

each R^g is independently selected from the group consisting of: hydrogen, and C₁₋₆alkyl;

m is an integer from 1 to 3;

20 n is an integer from 0 to 3;

p is an integer from 1 to 3;

q is an integer from 1 to 2;

r is an integer from 0 to 2;

s is an integer from 0 to 4;

25 t is an integer from 0 to 8;

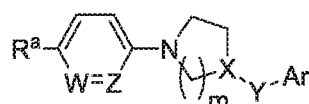
d is an integer from 0 to 2; and

e is an integer from 0 to 2,

provided that d + e is 2.

30 Compounds of Formula (XXV) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2011/011872. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2011/011872, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXVI,



(XXVI)

or a pharmaceutically acceptable salt thereof, wherein

each n is independently 0, 1 or 2;

each p is independently 0, 1, or 2;

m is 1, 2, or 3;

W and Z are each independently CH or N, with the proviso that at least one of W and Z is N;

X-Y is N-C(O), N-S(O)₂, N-CR¹R², CH-O, CH-S(O)_p, CH-NR⁵, or CH-CR¹R²;

Ar is phenyl, benzyl, naphthyl, or heteroaryl each of which is optionally substituted with one to five

5 R³ substituents;

R^a is phenyl, naphthyl, or a heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl,

isothiazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,

10 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, indolyl, benzthiazolyl, benzoxazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, and imidazo[1,2- α]pyridyl;

wherein phenyl, naphthyl, and the heteroaromatic ring are optionally substituted with one to three substituents independently selected from R⁶;

R¹ and R² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted
15 with one to three substituents independently selected from halogen and hydroxy;

each R⁶ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₄alkenyl, (CH₂)_nOR⁴, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC $\equiv$ N, (CH₂)_nCO₂R⁴, (CH₂)_nOC(O)R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴,
20 (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nO(CH₂)_nP(=O)(OR⁴)₂, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines;

25 and wherein any methylene (CH₂) carbon atom in R⁶ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R³ is independently selected from the group consisting of: C₁₋₆alkyl, (CH₂)_nOR⁴,
30 (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC $\equiv$ N, (CH₂)_nCO₂R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴, (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nO(CH₂)_nP(=O)(OR⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

35 in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two
40 substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -naphthyl, and $(CH_2)_n C_{3-7}$ cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC $_{1-4}$ alkyl; and

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one to five fluorines.

Compounds of Formula (XXVI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/009236. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/009236, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXVII,

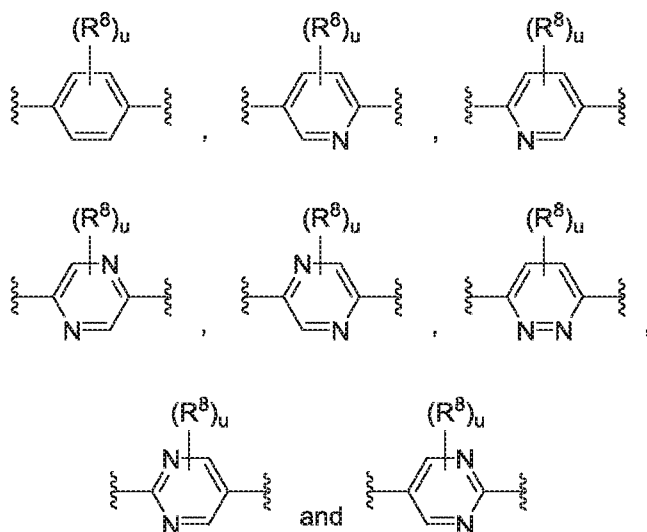
HetAr-W-X-Ar

(XXVII)

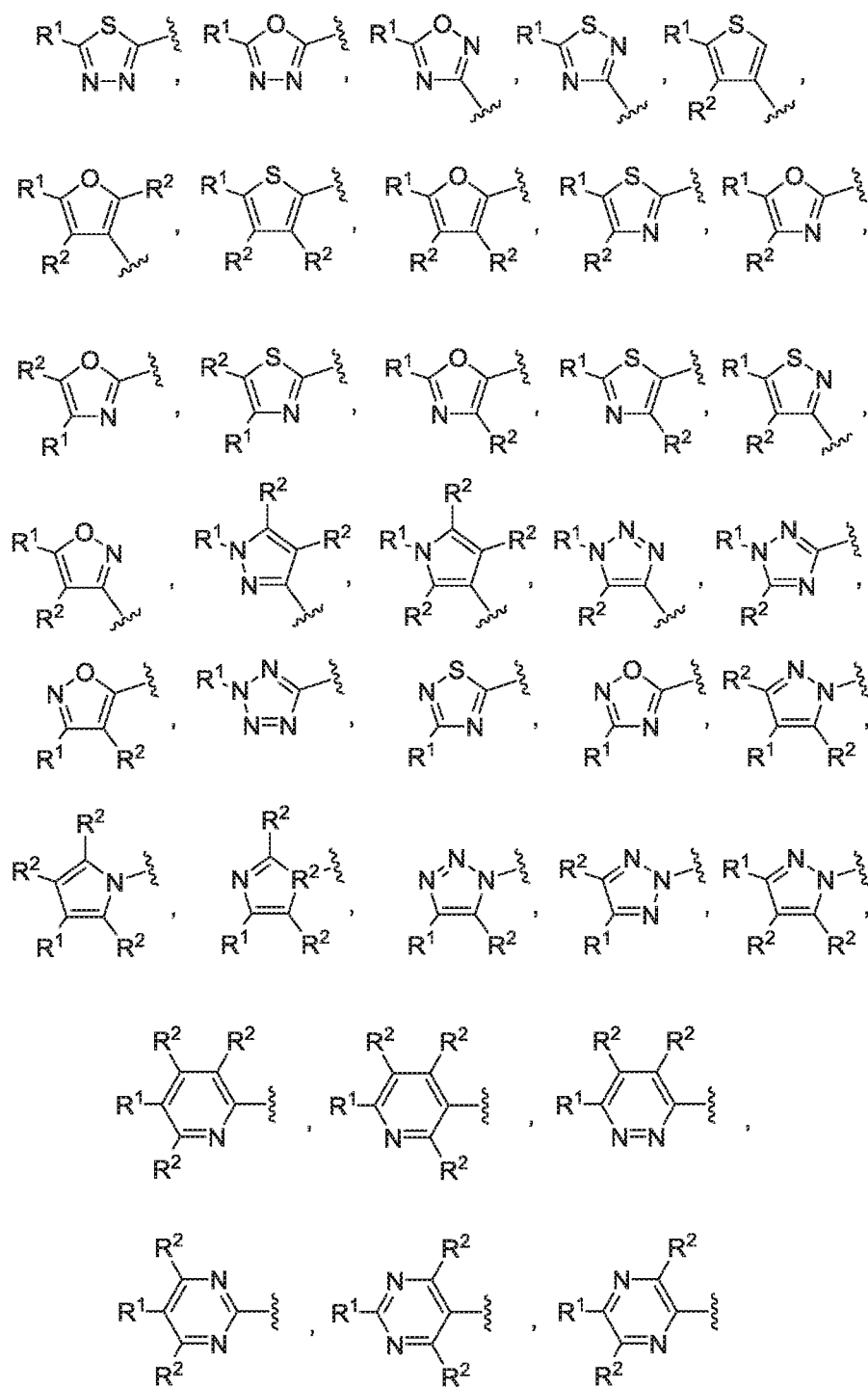
or a pharmaceutically acceptable salt thereof; wherein

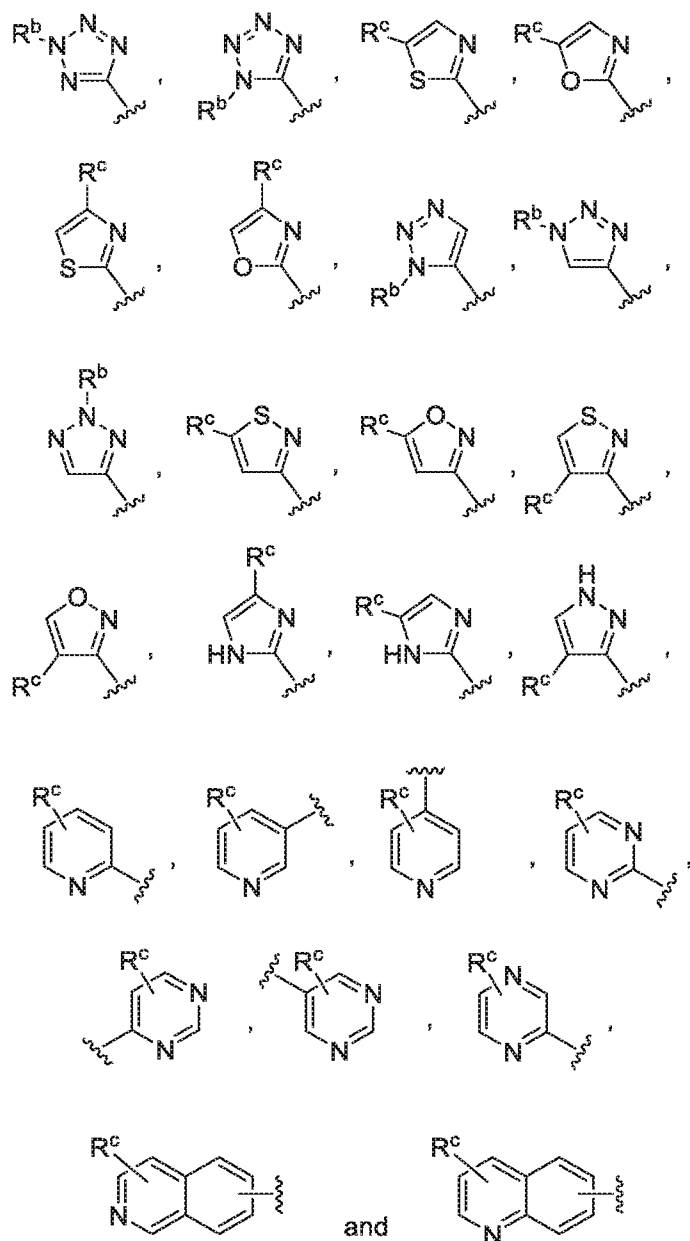
X is -O-, -S-, -S(O)-, -S(O) $_2$ -, -NR ^{9} -, or -CR ^{10} R ^{11} ;

W is selected from the group consisting of:



HetAr is heteroaryl selected from the group consisting of:





wherein

R^b is $-(CH_2)_iCO_2H$, $-(CH_2)_iCO_2C_{1-3}alkyl$, $-(CH_2)_i-Z-(CH_2)_pCO_2H$, or $-(CH_2)_i-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

5 R^c is $-(CH_2)_mCO_2H$, $-(CH_2)_mCO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_pCO_2H$, or $-(CH_2)_m-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

and wherein said R^1 heteroaryl ring is optionally substituted with a substituent selected from the group consisting of cyano, halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylthio$, $C_{1-4}alkylsulfonyl$, and trifluoromethyl;

10 each R^2 is independently selected from the group consisting of:

hydrogen,

halogen,

hydroxy,

cyano,

15 ammo,

nitro,

C₁₋₄alkyl, optionally substituted with one to five fluorines,
 C₁₋₄alkoxy, optionally substituted with one to five fluorines,
 C₁₋₄alkylthio, optionally substituted with one to five fluorines,
 C₁₋₄alkylsulfonyl,
 5 carboxy,
 C₁₋₄alkyloxycarbonyl, and
 C₁₋₄alkylcarbonyl;

Ar is phenyl or naphthyl optionally substituted with one to five R³ substituents; each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl, (CH₂)_n-phenyl,
 10 (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_n-C₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴,
 (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)₀₋₂R⁴,
 (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴,
 O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl, (CH₂)_s-Z-(CH₂)_t-heteroaryl,
 (CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl, (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂,
 15 (CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂,
 (CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂,
 (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃,
 and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with
 20 one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl,
 trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally
 substituted with one to two groups independently selected from fluorine, hydroxy, and

C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with
 the carbon atom to which they are attached to form a cyclopropyl group;

25 Z is O, S, or NR⁴;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl,
 (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_n-C₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three
 groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the
 30 atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally
 containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

each R⁶ and R⁷ are independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted
 with one to five fluorines;

each R⁸ is independently selected from the group consisting of hydrogen, halogen, and C₁₋₄alkyl
 35 wherein alkyl is optionally substituted with one to five fluorines;

R⁹, R¹⁰, and R¹¹ are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally
 substituted with one to five fluorines;

u is an integer from 0 to 2;

r is an integer from 0 to 3;

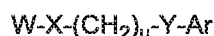
40 m is an integer from 1 to 3;

each p is independently an integer from 1 to 3;

each n is independently an integer from 0 to 2;
 each s is independently an integer from 1 to 3; and
 each t is independently an integer from 1 to 3.

Compounds of Formula (XXVII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/073973. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/073973, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXVIII,

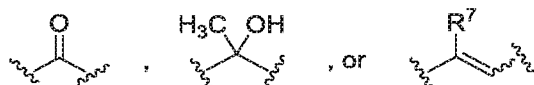


(XXVIII)

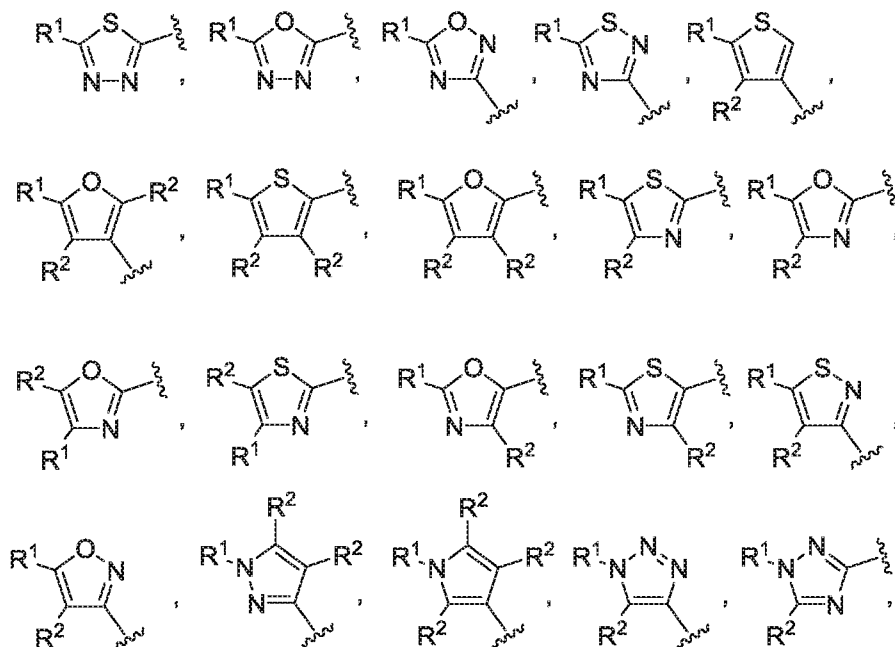
or a pharmaceutically acceptable salt thereof; wherein

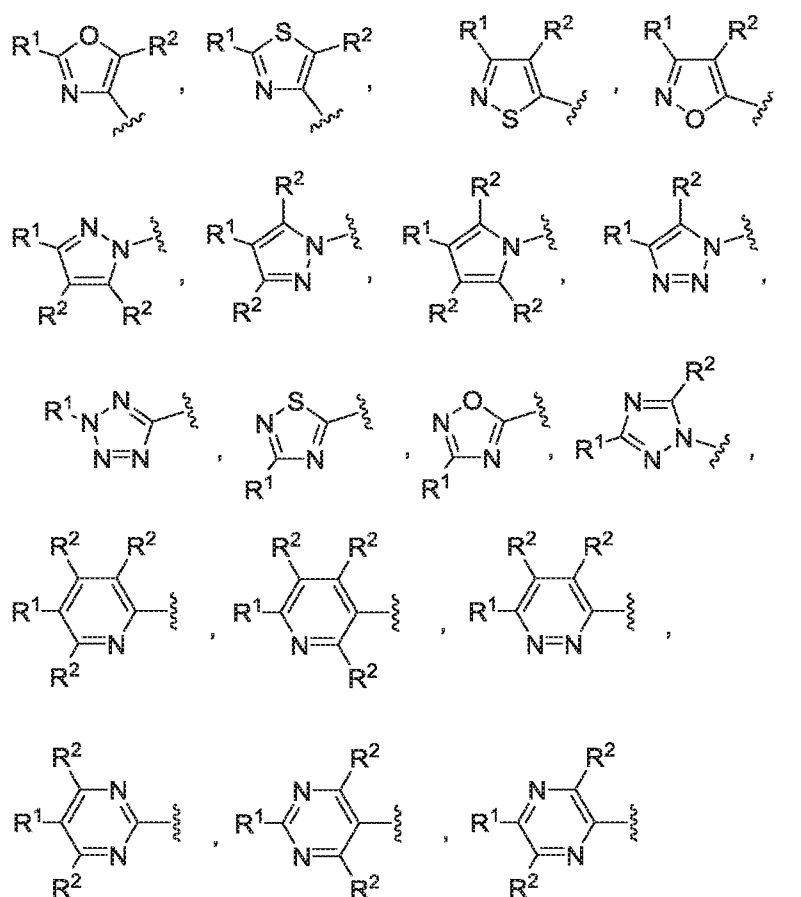
any methylene (CH₂) carbon atom in (CH₂)_u is optionally substituted with one to two R⁵ substituents independently selected from fluorine, hydroxy, oxo, hydroxymethyl, and C₁₋₄alkyl; or two R⁵ substituents, when on the same (CH₂) carbon atom, are taken together with the carbon atom to which they are attached to form a C₃₋₆cycloalkyl group; or any two methylene (CH₂) carbon atoms are taken together to form a saturated or monounsaturated five- or six-membered cycloalkyl group;

X and Y are each independently a bond, -O-, -S-, -S(O)-, -S(O)₂-, -NR⁶-,

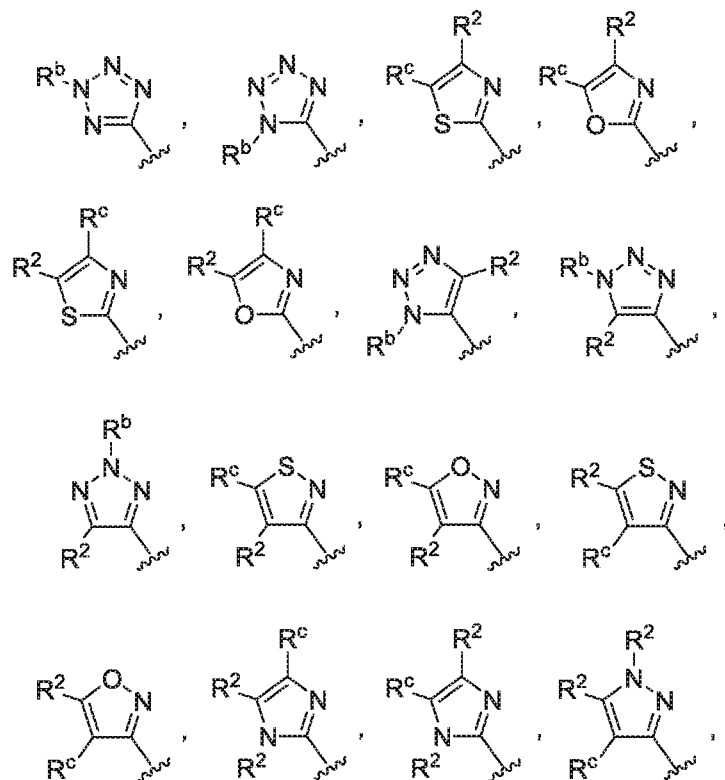


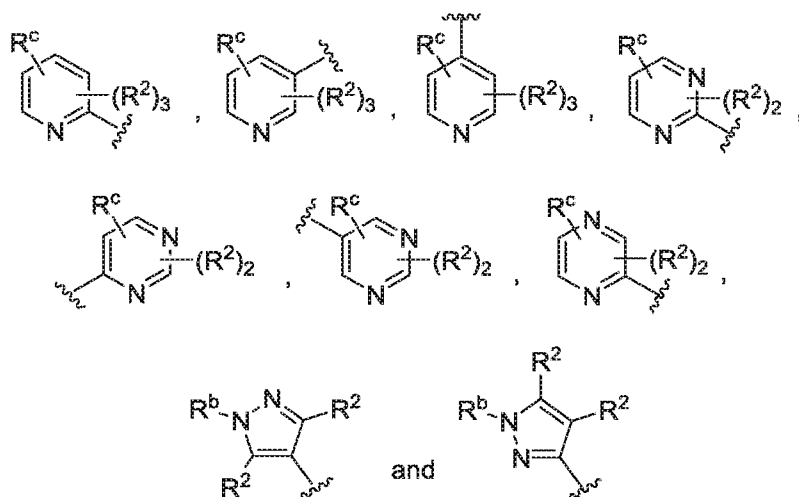
W is heteroaryl selected from the group consisting of:





R¹ is heteroaryl selected from the group consisting of:





wherein

R^b is $-(CH_2)_iCO_2H$, $-(CH_2)_iCO_2C_{1-3}alkyl$, $-(CH_2)_i-Z-(CH_2)_pCO_2H$, or $-(CH_2)_i-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

R^c is $-(CH_2)_mCO_2H$, $-(CH_2)_mCO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_pCO_2H$, or

5 $-(CH_2)_m-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

and wherein said R^1 heteroaryl ring is optionally substituted with one substituent independently selected from the group consisting of cyano, halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylthio$, $C_{1-4}alkylsulfonyl$, and trifluoromethyl;

each R^2 is independently selected from the group consisting of:

10 hydrogen,

halogen,

hydroxy,

cyano,

amino,

15 nitro,

$C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkoxy$, optionally substituted with one to five fluorines,

$C_{1-4}alkylthio$, optionally substituted with one to five fluorines,

$C_{1-4}alkylsulfonyl$,

20 carboxy,

$C_{1-4}alkyloxycarbonyl$, and

$C_{1-4}alkylcarbonyl$;

Ar is phenyl or naphthyl optionally substituted with one to five R^3 substituents; each R^3 is independently selected from the group consisting of: $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $(CH_2)_n$ -phenyl,

25 $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_n$ - C_{3-7} -cycloalkyl, halogen, nitro, $(CH_2)_nOR^4$,

$(CH_2)_nN(R^4)_2$, $(CH_2)_nC\equiv N$, $(CH_2)_nCO_2R^4$, $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_{0-2}R^4$,

$(CH_2)_nNR^4C(O)N(R^4)_2$, $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, $(CH_2)_nC(O)R^4$,

$O(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_s-Z-(CH_2)_t$ -phenyl, $(CH_2)_s-Z-(CH_2)_t$ -naphthyl, $(CH_2)_s-Z-(CH_2)_t$ -heteroaryl,

$(CH_2)_s-Z-(CH_2)_t$ -heterocyclyl, $(CH_2)_s-Z-(CH_2)_t$ - C_{3-7} -cycloalkyl, $(CH_2)_s-Z-(CH_2)_tOR^4$, $(CH_2)_s-Z-(CH_2)_tN(R^4)_2$,

30 $(CH_2)_s-Z-(CH_2)_tNR^4SO_2R^4$, $(CH_2)_s-Z-(CH_2)_tC\equiv N$, $(CH_2)_s-Z-(CH_2)_tCO_2R^4$, $(CH_2)_s-Z-(CH_2)_tSO_2N(R^4)_2$,

$(CH_2)_s-Z-(CH_2)_tS(O)_{0-2}R^4$, $(CH_2)_s-Z-(CH_2)_tNR^4C(O)N(R^4)_2$, $(CH_2)_s-Z-(CH_2)_tC(O)N(R^4)_2$,

$(\text{CH}_2)_s\text{-Z-(CH}_2)_t\text{-NR}^4\text{C(O)R}^4$, $(\text{CH}_2)_s\text{-Z-(CH}_2)_t\text{-NR}^4\text{CO}_2\text{R}^4$, $(\text{CH}_2)_s\text{-Z-(CH}_2)_t\text{-C(O)R}^4$, CF_3 , CH_2CF_3 , OCF_3 , and OCH_2CF_3 ;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy optionally substituted with one to five fluorines; and wherein any methylene (CH_2) carbon atom in R^3 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(\text{CH}_2)_n\text{-phenyl}$, $(\text{CH}_2)_n\text{-heteroaryl}$, $(\text{CH}_2)_n\text{-naphthyl}$, and $(\text{CH}_2)_n\text{C}_{3-7}\text{cycloalkyl}$;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC_{1-4} alkyl;

each R^6 and R^7 are independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to five fluorines;

u is an integer from 1 to 4;

r is an integer from 1 to 3;

m is an integer from 0 to 3;

each p is independently an integer from 1 to 3;

each n is independently an integer from 0 to 2;

each s is independently an integer from 1 to 3; and

each t is independently an integer from 1 to 3.

Compounds of Formula (XXVIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/128335. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/128335, the compounds of which are herein incorporated by reference.

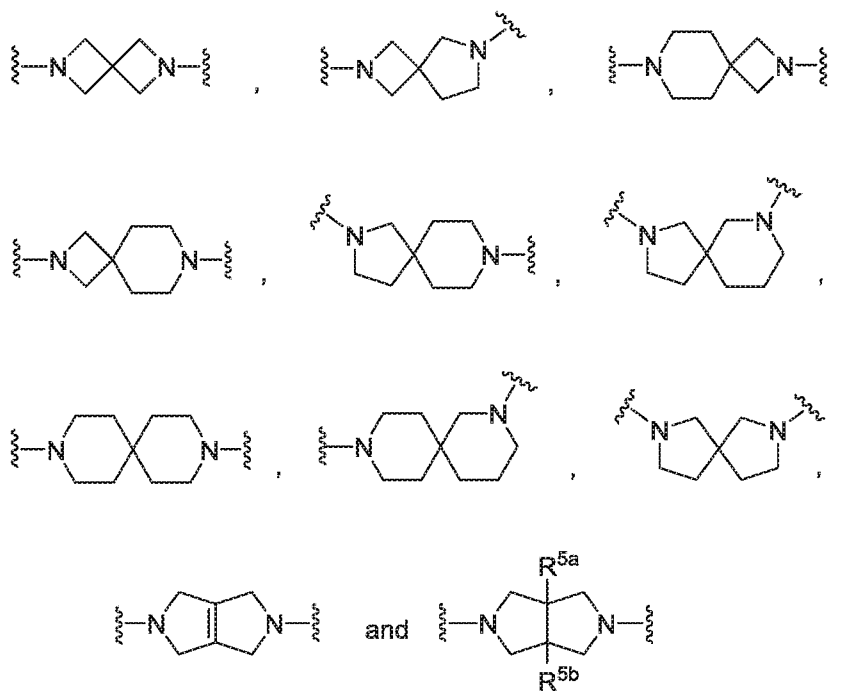
In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXIX,

W-Het-Ar

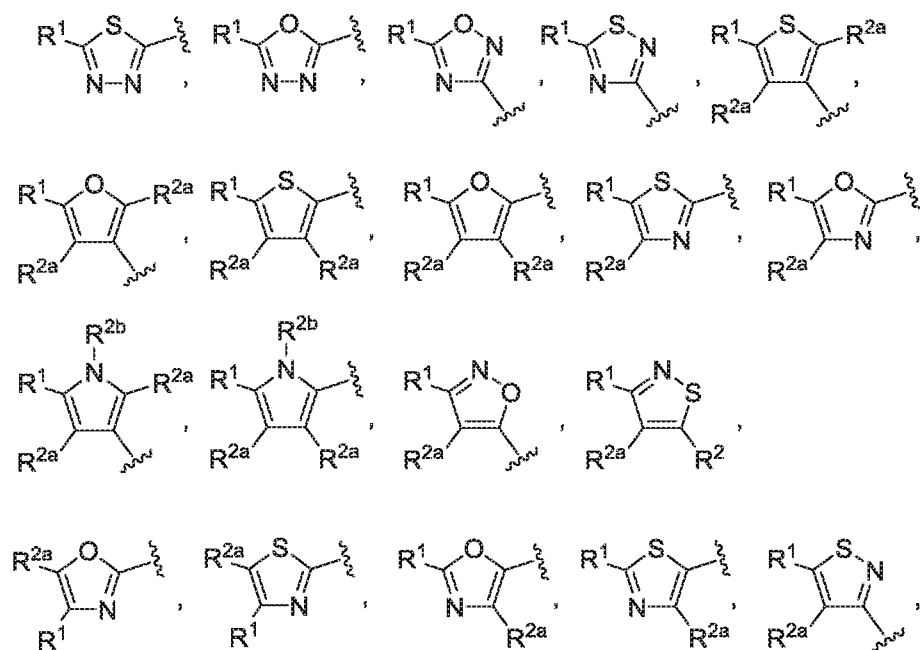
(XXIX)

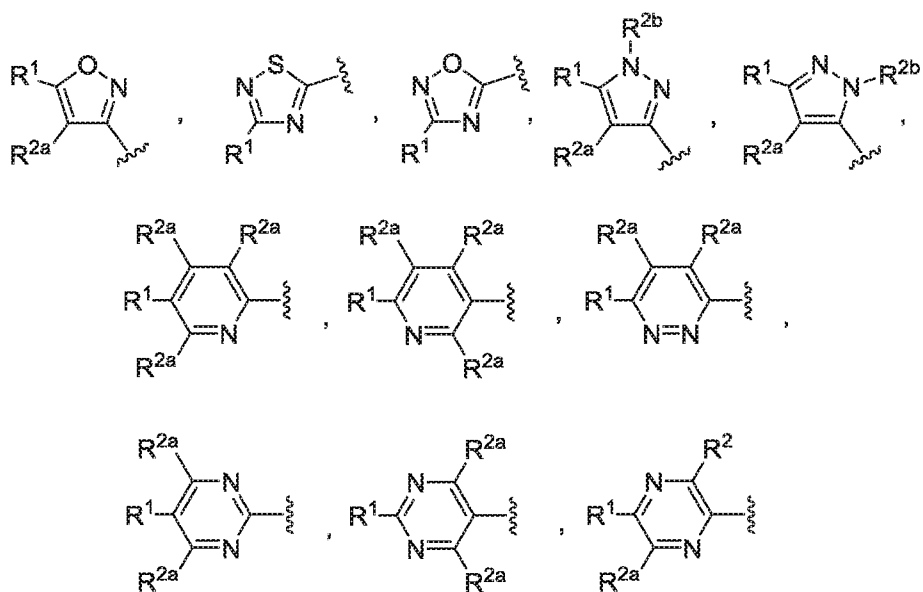
or a pharmaceutically acceptable salt thereof; wherein

Het is a heterobicyclic ring system selected from the group consisting of:

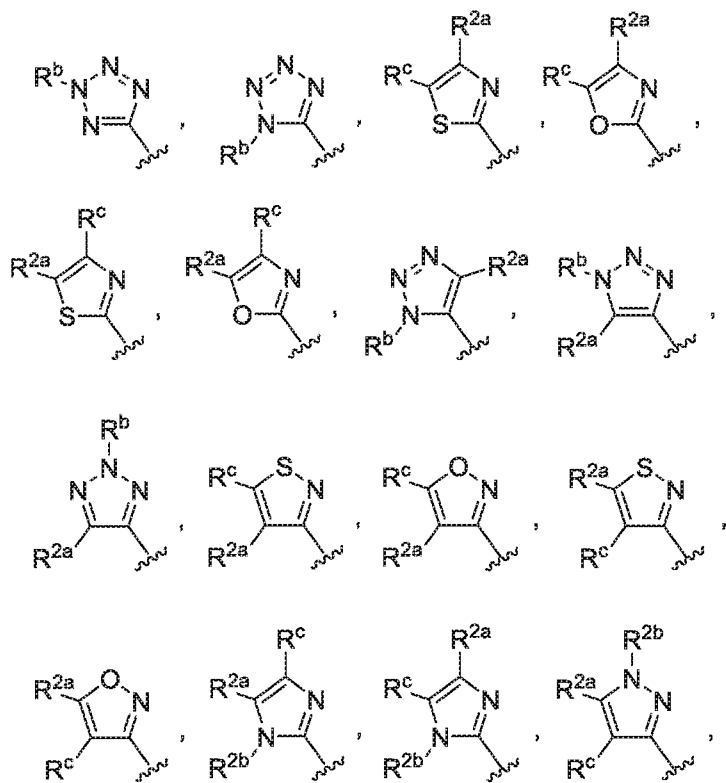


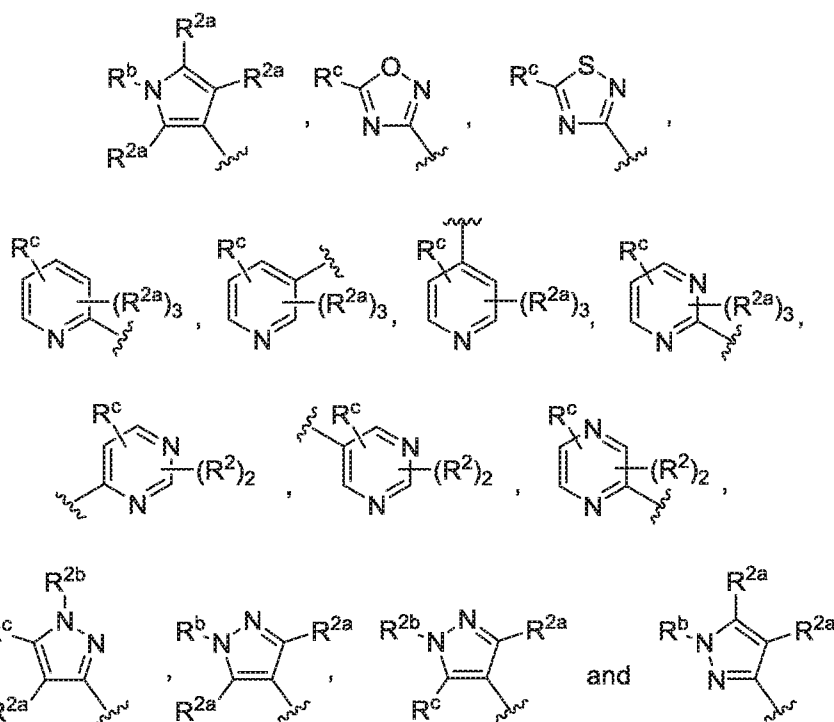
W is heteroaryl selected from the group consisting of:





R¹ is heteroaryl selected from the group consisting of:





wherein

R^b is $-(CH_2)_rCO_2H$, $-(CH_2)_rCO_2C_{1-3}alkyl$, $-(CH_2)_r-Z-(CH_2)_pCO_2H$, or $-(CH_2)_r-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

R^c is $-(CH_2)_mCO_2H$, $-(CH_2)_mCO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_pCO_2H$, or

5 $-(CH_2)_m-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

Z is O, $S(O)_q$, or NR^4 ;

each R^{2a} is independently selected from the group consisting of:

hydrogen,

halogen,

10 hydroxy,

cyano,

$C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkoxy$, optionally substituted with one to five fluorines,

$C_{1-4}alkylthio$, optionally substituted with one to five fluorines,

15 $C_{1-4}alkylsulfonyl$, optionally substituted with one to five fluorines,

carboxy,

$C_{1-4}alkyloxycarbonyl$, and

$C_{1-4}alkylcarbonyl$;

each R^{2b} is independently selected from the group consisting of:

20 hydrogen,

$C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkylsulfonyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkyloxycarbonyl$, and

$C_{1-4}alkylcarbonyl$;

25 Ar is phenyl, naphthyl, thienyl, or pyridyl optionally substituted with one to five R^3 substituents;

each R^3 is independently selected from the group consisting of:

halogen,

cyano,

C₁₋₆alkyl, optionally substituted with one to five fluorines,

C₁₋₆alkoxy, optionally substituted with one to five fluorines,

-OCH₂C₃₋₆ cycloalkyl,

C₁₋₆alkylthio, optionally substituted with one to five fluorines,

C₁₋₆alkylsulfonyl, optionally substituted with one to five fluorines, and

phenyl, optionally substituted with one to three substituents independently selected

from halogen, C₁₋₄alkyl, cyano, trifluoromethyl, and trifluoromethoxy;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl; wherein alkyl, phenyl, heteroaryl, naphthyl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy;

R^{5a} and R^{5b} are each independently selected from the group consisting of:

hydrogen,

fluorine,

hydroxy,

C₁₋₃alkyl, optionally substituted with one to five fluorines, and

C₁₋₄alkylcarbonyloxy;

m is an integer from 0 to 3;

n is an integer from 0 to 2;

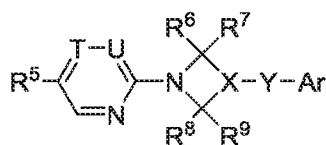
p is an integer from 1 to 3;

q is an integer from 0 to 2; and

r is an integer from 1 to 3.

Compounds of Formula (XXIX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2010/108268. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2010/108268, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXX,



(XXX)

or a pharmaceutically acceptable salt thereof; wherein

X-Y is CH-O, CH-S or CH-CR¹R²;

each of U and T is CH or N, with the proviso that at least one of U and T is N;

Ar is phenyl, benzyl, naphthyl, or pyridyl each of which is optionally substituted with one to five substituents independently selected from R³;

R^1 and R^2 are each independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R^5 is independently selected from the group consisting of: $(CH_2)_nCO_2R^4$, $(CH_2)_nOC(O)R^4$,

$(CH_2)_nCOR^4$, $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_qR^4$, $(CH_2)_nNR^4C(O)N(R^4)_2$,

5 $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nC(O)N(OR^4)R^4$, $(CH_2)_nC(O)NR^4NC(O)R^4$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, and $O(CH_2)_nC(O)N(R^4)_2$;

wherein any methylene (CH_2) carbon atom in R^5 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five

10 fluorines; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^3 is independently selected from the group consisting of:

halogen,

C_{1-6} alkyl, optionally substituted with one to five fluorines,

$(CH_2)_nOR^4$,

15 $(CH_2)_nN(R^4)_2$,

$(CH_2)_nC\equiv N$,

$(CH_2)_nCOR^4$, and

$(CH_2)_nS(O)_qR^4$;

wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any

20 methylene (CH_2) carbon atom in R^3 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five fluorines; or two

substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(CH_2)_m$ -phenyl,

25 $(CH_2)_m$ -heteroaryl, $(CH_2)_m$ -naphthyl, and $(CH_2)_mC_{3-7}$ cycloalkyl;

wherein alkyl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, cyano, $-C_{1-4}$ alkoxy, $-C_{1-4}$ alkylthio, $-C_{1-4}$ alkylsulfonyl, $-carboxy$, and

$-CO_2C_{1-4}$ alkyl; and wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from the group consisting of:

30 halogen,

C_{1-4} alkyl, optionally substituted with one to five fluorines,

C_{1-4} alkoxy, optionally substituted with one to five fluorines,

C_{1-4} alkylthio, optionally substituted with one to five fluorines,

C_{1-4} alkylsulfonyl, optionally substituted with one to five fluorines,

35 C_{1-4} alkylcarbonyl,

C_{1-4} alkyloxycarbonyl,

amino,

mono- $(C_{1-4}$ alkyl)amino,

di- $(C_{1-4}$ alkyl)amino,

40 $-O(CH_2)_pCO_2H$,

$-O(CH_2)_pCO_2C_{1-4}$ alkyl,

- S(O)_q(CH₂)_pCO₂H,
- S(O)_q(CH₂)_pCO₂C₁₋₄alkyl,
- NH(CH₂)_pCO₂H,
- NH(CH₂)_pCO₂C₁₋₄alkyl,
- (CH₂)_pCO₂H,
- (CH₂)_pCO₂C₁₋₄alkyl,
- N(R¹⁰)C(O)(R¹⁰),

phenyl, optionally substituted with one to two substituents selected from halogen, carboxy, and C₁₋₄alkyl, and heteroaryl, optionally substituted with one to two substituents selected from halogen, carboxy, and C₁₋₄alkyl;

or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄alkyl;

each n is independently an integer from 0 to 2;

each m is independently an integer from 0 to 2;

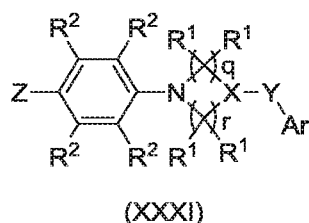
each p is independently an integer from 1 to 3;

each q is independently an integer from 0 to 2:

R⁶, R⁷, R⁸, and R⁹ are each independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; and each R¹⁰ is independently hydrogen or C₁₋₄alkyl optionally substituted with one to five fluorines.

Compounds of Formula (XXX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2010/043052. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2010/043052, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXI.



or a pharmaceutically acceptable salt thereof; wherein

q is 1 or 2:

r is 1 or 2:

each n is independently 0, 1 or 2:

each m is independently 0, 1, or 2:

each p is independently 0, 1, or 2;

X-Y is N-C(O), N-S(O)₂, N-CR^aR^b, CH-O, CH-S(O)₂, CH-NR⁵, or CH-CR^aR^b;

Ar is phenyl, naphthyl, or heteroaryl each of which is optionally substituted with one to five R⁶ groups:

Z is phenyl, naphthyl, or a heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, indolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, and imidazo[1,2- α]pyridyl;

wherein phenyl, naphthyl, and the heteroaromatic ring are optionally substituted with one to three substituents independently selected from R³;

R^a and R^b are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R² is independently selected from the group consisting of:

hydrogen,

halogen,

hydroxy,

cyano,

amino,

nitro,

C₁₋₄alkyl, optionally substituted with one to five fluorines,

C₁₋₄alkoxy, optionally substituted with one to five fluorines,

C₁₋₄alkylthio, optionally substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,

carboxy,

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

each R³ is independently selected from the group consisting of: C¹⁻⁶alkyl, C²⁻⁴alkenyl, (CH₂)_nOR⁴, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nOC(O)R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴, (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nOCH₂P(=O)(OR⁴)₂, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_m-phenyl, (CH₂)_m-heteroaryl, (CH₂)_m-naphthyl, and (CH₂)_mC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy, wherein alkyl and alkoxy are

optionally substituted with one to five fluorines; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄alkyl;

each R¹ is independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

R⁵ is hydrogen or C₁₋₆alkyl; and

each R⁶ is independently selected from the group consisting of: C₁₋₆alkyl, (CH₂)_nOR⁴, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴, (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₃₋₆ cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH₂) carbon atom in R⁶ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group.

Compounds of Formula (XXXI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/134457. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/134457, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXIII,



(XXXII)

or a pharmaceutically acceptable salt thereof; wherein

X-Y is N-C(O), N-CR¹R², CH-O, CH-S(O)_p, CH-NR¹⁰, or CH-CR¹R²;

Ar is phenyl, benzyl, naphthyl, or pyridyl each of which is optionally substituted with one to five substituents independently selected from R³;

HetAr represents a heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridazinyl, pyridinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridazinyl, pyridinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazolyl,

in which the heteroaromatic ring is optionally substituted with one to two substituents independently selected from R⁵;

R^1 and R^2 are each independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R^5 is independently selected from the group consisting of: C_{1-6} alkyl, C_{2-4} alkenyl, $(CH_2)_nOR^4$, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_nC_{3-7}$ cycloalkyl, halogen, $(CH_2)_nN(R^4)_2$, $(CH_2)_nO=N$, $(CH_2)_nCO_2R^4$, $(CH_2)_nOC(O)R^4$, $(CH_2)_nCOR^4$, NO_2 , $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_pR^4$, $(CH_2)_nNR^4C(O)N(R^4)_2$, $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nC(O)N(OR^4)R^4$, $(CH_2)_nC(O)N(NH_2)R^4$, $(CH_2)_nC(O)NR^4NC(O)R^4$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, $(CH_2)_nP(=O)(OR^4)_2$, $(CH_2)_nOP(=O)(OR^4)_2$, $(CH_2)_nO(CH_2)_nP(=O)(OR^4)_2$, $O(CH_2)_nC(O)N(R^4)_2$, CF_3 , CH_2CF_3 , OCF_3 , and OCH_2CF_3 ;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{3-6} cycloalkyl, carboxy- C_{1-3} alkyl, C_{1-3} alkyloxycarbonyl- C_{1-3} alkyl, and C_{1-4} alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH_2) carbon atom in R^5 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^3 is independently selected from the group consisting of: C_{1-6} alkyl, $(CH_2)_nOR^4$, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_nC_{3-7}$ cycloalkyl, halogen, $(CH_2)_nN(R^4)_2$, $(CH_2)_nC\equiv N$, $(CH_2)_nCO_2R^4$, $(CH_2)_nCOR^4$, NO_2 , $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_pR^4$, $(CH_2)_nNR^4C(O)N(R^4)_2$, $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nC(O)N(OR^4)R^4$, $(CH_2)_nC(O)N(NH_2)R^4$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, $O(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nP(=O)(OR^4)_2$, $(CH_2)_nOP(=O)(OR^4)_2$, $(CH_2)_nO(CH_2)_nP(=O)(OR^4)_2$, CF_3 , CH_2CF_3 , OCF_3 , and OCH_2CF_3 ;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkoxy, C_{3-6} cycloalkyl, and C_{1-4} alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH_2) carbon atom in R^3 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(CH_2)_m$ -phenyl, $(CH_2)_m$ -heteroaryl, $(CH_2)_m$ -naphthyl, and $(CH_2)_mC_{3-7}$ cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC C_{1-4} alkyl;

each n is independently 0, 1 or 2;

each p is independently 0, 1, or 2;

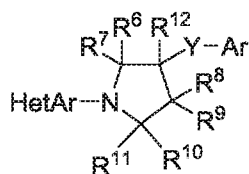
each m is independently 0, 1 or 2;

R^6 , R^7 , R^8 , and R^9 are each independently hydrogen, fluorine, or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; and

R^{10} is hydrogen or C_{1-6} alkyl optionally substituted with one to five fluorines.

Compounds of Formula (XXXII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/143823. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/143823, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXIII,



(XXXIII)

or a pharmaceutically acceptable salt thereof; wherein

Y is O, $S(O)_p$, or CR^1R^2 ;

Ar is phenyl, benzyl, naphthyl, or pyridyl each of which is optionally substituted with one to five substituents independently selected from R^3 ;

HetAr is a heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, benzthiazolyl, benzoxazolyl, benzimidazolyl, benzisoxazolyl, and benzisothiazolyl;

in which the heteroaromatic ring is optionally substituted with one to two substituents independently selected from R^5 ;

R^1 and R^2 are each independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R^3 is independently selected from the group consisting of: C_{1-6} alkyl, $(CH_2)_nOR^4$, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_nC_{3-7}$ cycloalkyl, halogen, $(CH_2)_nN(R^4)_2$, $(CH_2)_nC\equiv N$, $(CH_2)_nCO_2R^4$, $(CH_2)_nCOR^4$, NO_2 , $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_pR^4$, $(CH_2)_nNR^4C(O)N(R^4)_2$, $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nC(O)N(OR^4)R^4$, $(CH_2)_nC(O)N(NH_2)R^4$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, $O(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nP(=O)(OR^4)_2$, $(CH_2)_nOP(=O)(OR^4)_2$, $(CH_2)_nO(CH_2)_nP(=O)(OR^4)_2$, CF_3 , CH_2CF_3 , OCF_3 , and OCH_2CF_3 ;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkoxy, C_{3-6} cycloalkyl, and C_{1-4} alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH_2) carbon atom in R^3 is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(CH_2)_m$ -phenyl, $(CH_2)_m$ -heteroaryl, $(CH_2)_m$ -naphthyl, and $(CH_2)_mC_{3-7}$ cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional

heteroatom selected from O, S, and NC₁₋₄alkyl;

each R⁵ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₄alkenyl, (CH₂)_nR⁴, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nOC(O)R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴, (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nC(O)NR⁴NC(O)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nO(CH₂)_nP(=O)(OR⁴)₂, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with carboxy, hydroxy, or one to three fluorines; and wherein any methylene (CH₂) carbon atom in R⁵ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxyl;

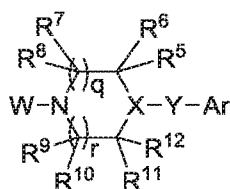
each n is independently 0, 1 or 2;

each m is independently 0, 1, or 2; and

p is 0, 1, or 2.

Compounds of Formula (XXXIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/143824. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/143824, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXIV,



(XXXIV)

or a pharmaceutically acceptable salt thereof; wherein

q is 0 or 1;

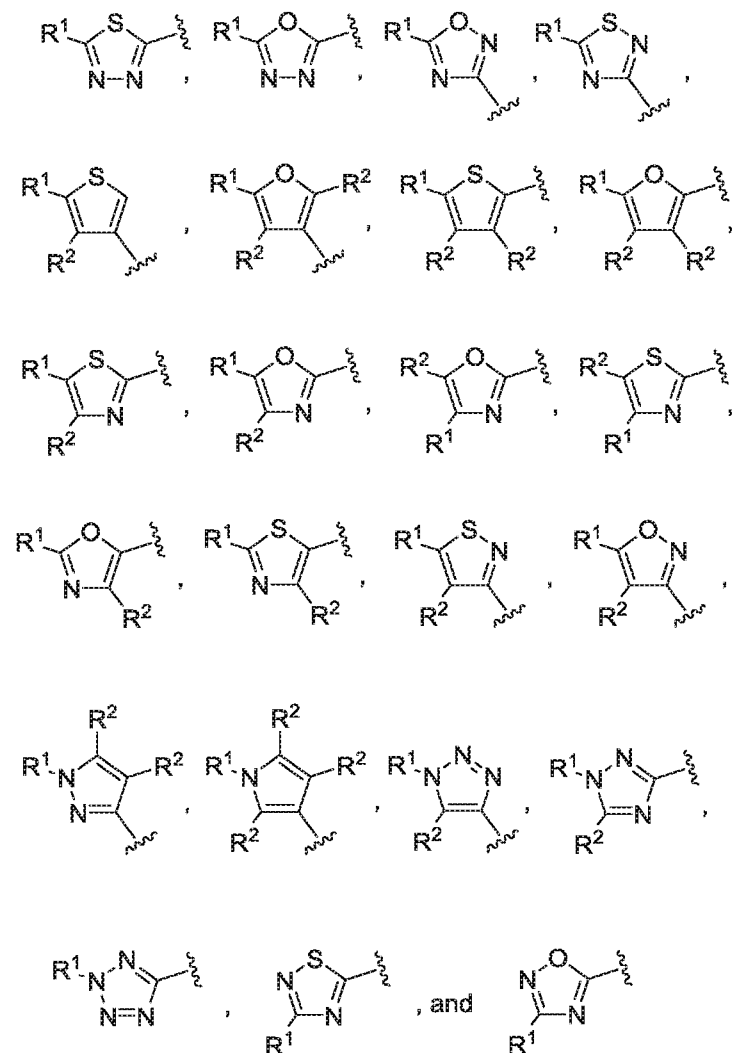
r is 0 or 1;

Z is O, S, or NR⁴;

X-Y is N-C(O), N-CR^aR^b, CR¹⁴-O, CR¹⁴-S(O)₀₋₂, or CR₁₃-CR^aR^b;

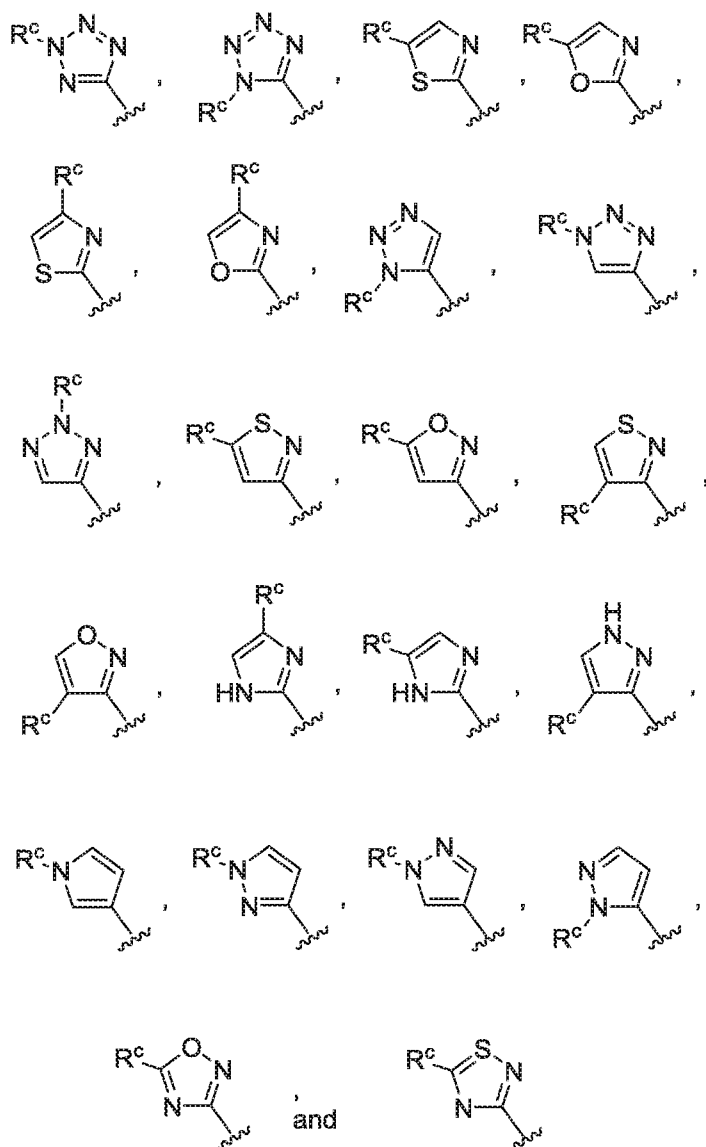
R^a and R^b are each independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

W is heteroaryl selected from the group consisting of:



5

R^1 is heteroaryl selected from the group consisting of:



wherein R^c is $-(CH_2)_mCO_2H$, $-(CH_2)_mCO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_pCO_2H$, or $-(CH_2)_m-Z-(CH_2)_pCO_2C_{1-3}alkyl$; wherein any methylene (CH_2) carbon atom in $(CH_2)_m$ or $(CH_2)_p$ is optionally substituted with one hydroxy, one amino, or one to two fluorines; and

5 wherein said R^1 heteroaryl ring is optionally substituted with one substituent independently selected from the group consisting of cyano, halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylthio$, $C_{1-4}alkylsulfonyl$, and trifluoromethyl;

each R^2 is independently selected from the group consisting of:

hydrogen,

10 halogen,

hydroxy,

cyano,

amino,

nitro,

15 $C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkoxy$, optionally substituted with one to five fluorines,

$C_{1-4}alkylthio$, optionally substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,
 carboxy,
 C₁₋₄alkyloxycarbonyl, and
 C₁₋₄alkylcarbonyl;

5 Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R³ substituents; each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)₀₋₂R⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴,
 10 O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl, (CH₂)_s-Z-(CH₂)_t-heteroaryl, (CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl, (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃,
 15 and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy, optionally substituted with one to five fluorines; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy,
 20 and C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three
 25 groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl,
 30 wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

R¹³ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy;

each R¹⁴ is hydrogen or C₁₋₃alkyl;

each m is independently an integer from 0 to 4;

each p is independently an integer from 1 to 3;

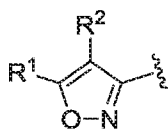
35 each n is independently an integer from 0 to 2;

each s is independently an integer from 1 to 3; and

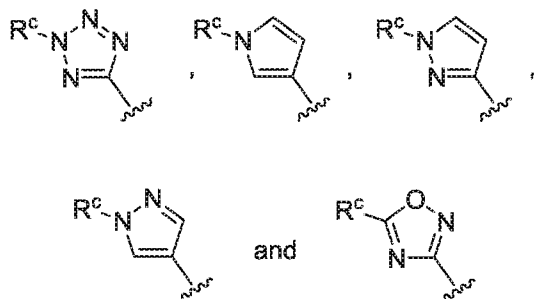
each t is independently an integer from 1 to 3.

In some embodiments of the compound of Formula XXXIV, R² is hydrogen.

In some embodiments of the compound of Formula XXXIV, W is

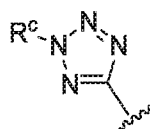


In some embodiments of the compound of Formula XXXIV, R^1 is heteroaryl selected from the group consisting of:



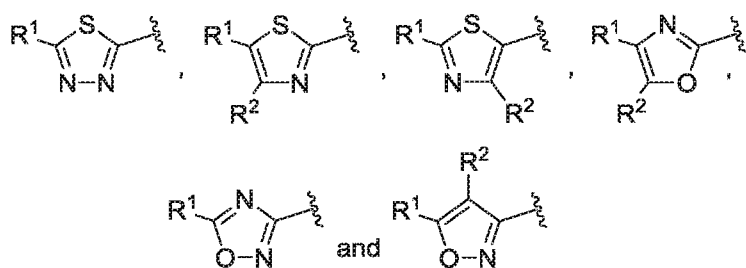
5 wherein R^c is $-\text{CH}_2\text{CO}_2\text{H}$ or $-\text{CH}_2\text{CO}_2\text{C}_{1-3}$ alkyl.

In some embodiments of the compound of Formula XXXIV, R^1 is

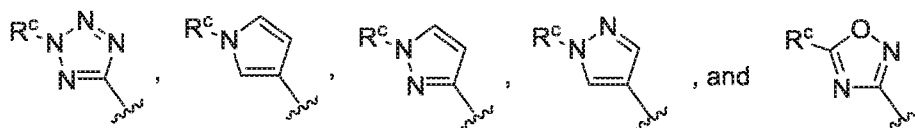


In some embodiments of the compound of Formula XXXIV, when q and r are both 1;
X-Y is CH-O;

10 W is heteroaryl selected from the group consisting of:

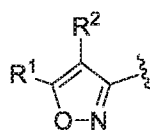


and R^1 is heteroaryl selected from the group consisting of:

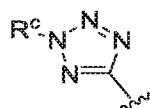


15 wherein R^c is $-\text{CH}_2\text{CO}_2\text{H}$ or $-\text{CH}_2\text{CO}_2\text{C}_{1-3}$ alkyl.

In some embodiments of the compound of Formula XXXIV, W is



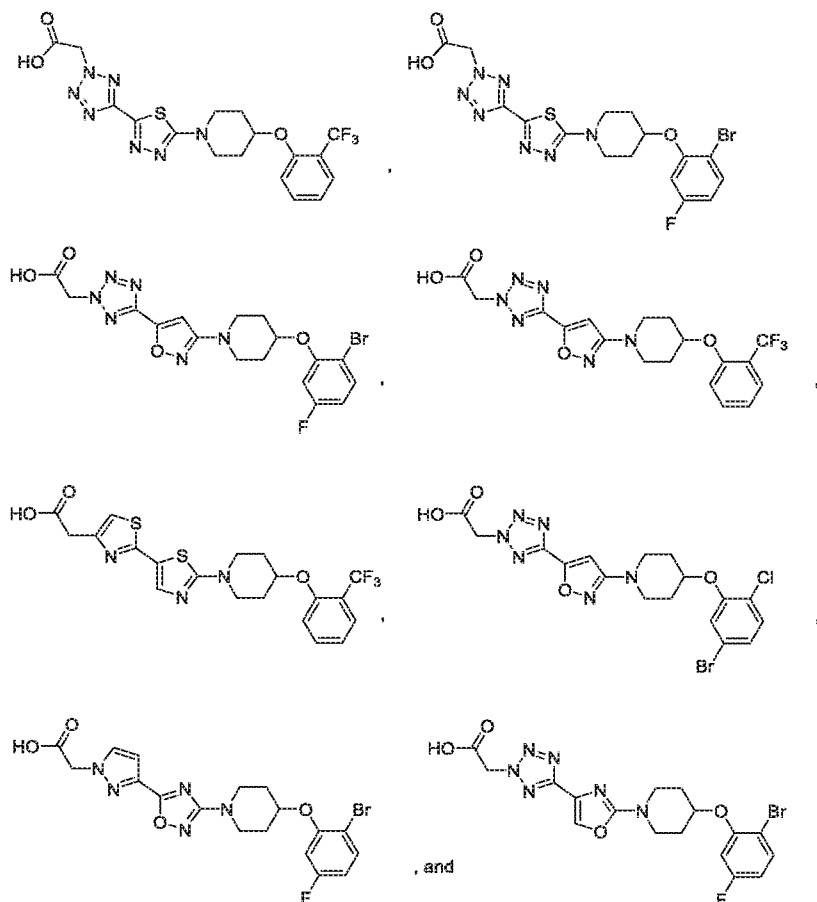
and R^1 is



wherein R^c is -CH₂CO₂H or -CH₂CO₂C₁₋₃alkyl.

In some embodiments of the compound of Formula XXXIV, R², R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each hydrogen.

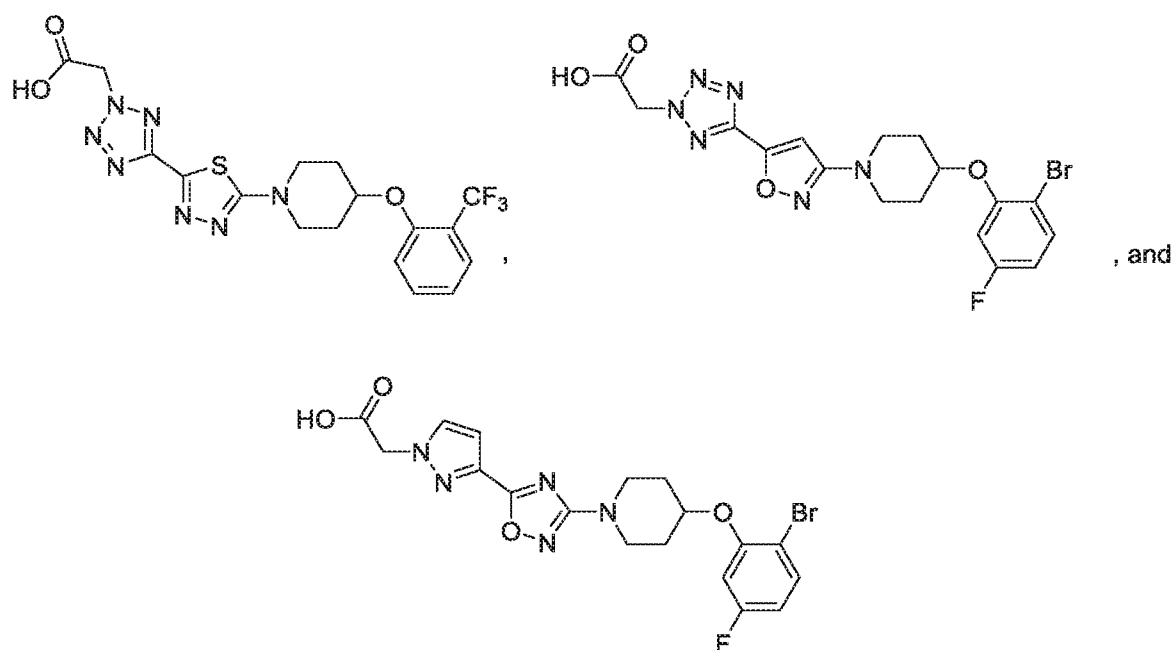
In some embodiments, the compound of Formula XXXIV is selected from:



5

or a pharmaceutically acceptable salt thereof.

In other embodiments of any of the foregoing methods, the SCD inhibitor is



In some embodiments, the compound of Formula XXXIV is selected from:

[5-(5-{4-[2-(Trifluoromethyl)phenoxy]piperidin-1-yl}-1,3,4-thiadiazol-2-yl)-2H-tetrazol-2-yl]acetic acid

[5-(5-{4-[2-(Trifluoromethyl)phenoxy]piperidin-1-yl}-1,3,4-thiadiazol-2-yl)-1-H-tetrazol-1-yl]acetic acid

(5-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-2H-tetrazol-2-yl)acetic acid

(5-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-1H-tetrazol-1-yl)acetic acid

(2'-{4-[2-(Trifluoromethyl)phenoxy]piperidin-1-yl}-2,5'-bi-1,3-thiazol-4-yl)acetic acid

(5-{3-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]isoxazol-5-yl}-2H-tetrazol-2-yl)acetic acid

(3-{3-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1H-pyrrol-1-yl)acetic acid

(3-{3-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1-yl)acetic acid

(5-{3-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1H-pyrazol-1-yl)acetic acid

(4-{3-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1H-pyrazol-1-yl)acetic acid

Sodium(5-{3-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-2H-tetrazol-2-yl)acetate

3-(3-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-1,2,4-oxadiazol-5-yl)propanoic acid

(5-{3-[4-(5-Bromo-2-chlorophenoxy)piperidin-1-yl]isoxazol-5-yl}-2H-tetrazol-2-yl)acetic acid

3-(3-{3-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]-1,2,4-oxadiazol-5-yl}-1H-pyrazol-1-yl)propanoic acid

(2R)-3-(3-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-1,2,4-oxadiazol-5-yl)-2-hydroxypropanoic acid

(2S)-3-(3-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-1,2,4-oxadiazol-5-yl)-2-hydroxypropanoic acid

3-(3-{5-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3,4-thiadiazol-2-yl}-1,2,4-oxadiazol-5-yl)-L-alanine

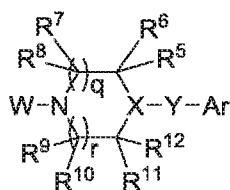
{5-[3-(4-{[4-Chloro-4'-(trifluoromethoxy)biphenyl-3-yl]oxy}piperidin-1-yl)isoxazol-5-yl]-2H-tetrazol-2-yl}acetic acid

(5-{2-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3-oxazol-4-yl}-2H-tetrazol-2-yl)acetic acid

(5-{2-[4-(2-Bromo-5-fluorophenoxy)piperidin-1-yl]-1,3-oxazol-4-yl}-1H-tetrazol-1-yl)acetic acid

Compounds of Formula (XXXIV) may be synthesized by methods known in the art, e.g., those described in U.S. Patent No. 8,063,224 B2. In some embodiments, the SCD inhibitor is a compound disclosed in U.S. Patent No. 8,063,224 B2, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXV,



(XXXV)

or a pharmaceutically acceptable salt thereof; wherein

each m is independently an integer from 0 to 4;

each n is independently an integer from 0 to 2;

5 each s is independently an integer from 1 to 3;

each t is independently an integer from 1 to 3;

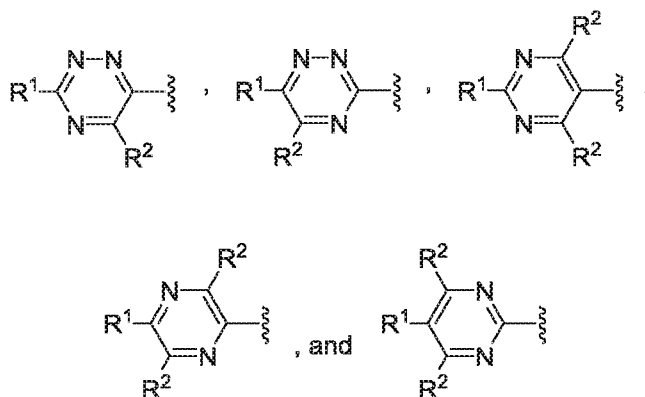
q is 0 or 1;

r is 0 or 1;

Z is O, S, or NR^4 ;

10 X-Y is $\text{N-CR}^a\text{R}^b$, $\text{CR}^{14}\text{-O}$, $\text{CR}^{14}\text{-S(O)}_{0-2}$, or $\text{CR}^{13}\text{-CR}^a\text{R}^b$;

W is heteroaryl selected from the group consisting of:

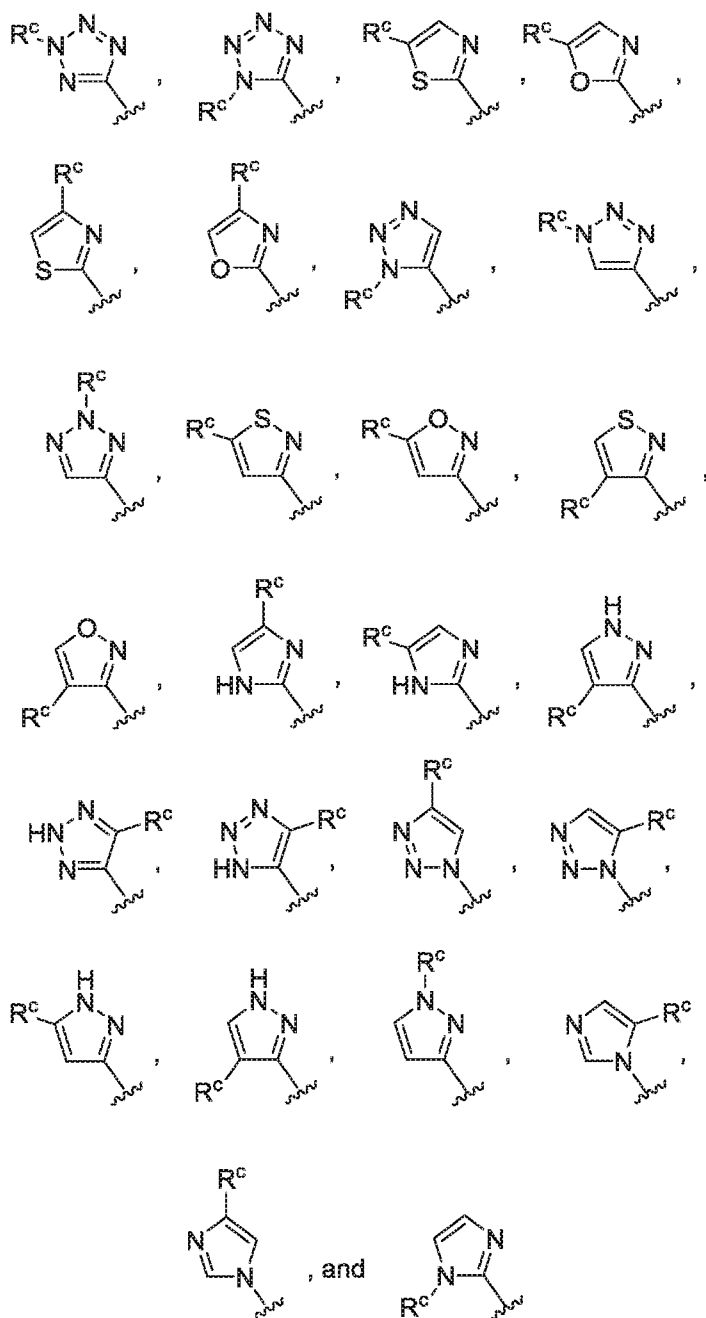


Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R^3 substituents;

R^a and R^b are each independently hydrogen or C_{1-3} alkyl, wherein alkyl is optionally substituted

15 with one to three substituents independently selected from fluorine and hydroxy;

R^1 is heteroaryl selected from the group consisting of:



wherein R^c is $-(CH_2)_m CO_2H$, $-(CH_2)_m CO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_p CO_2H$, or $-(CH_2)_m-Z-(CH_2)_p CO_2C_{1-3}alkyl$, wherein each (CH_2) methylene group is optionally substituted with one or two substituents selected from the group consisting of $C_{1-4}alkyl$, fluorine, oxo, and hydroxy; and wherein said R^1 heteroaryl ring is optionally substituted with one substituent independently selected from the group consisting of cyano, halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylthio$, $C_{1-4}alkylsulfonyl$, and trifluoromethyl;

each R^2 is independently selected from the group consisting of:

hydrogen,
halogen,
hydroxy,
cyano,
amino,

nitro,

C₁₋₄alkyl, optionally substituted with one to five fluorines,

C₁₋₄alkoxy, optionally substituted with one to five fluorines,

C₁₋₄alkylthio, optionally substituted with one to five fluorines,

5 C₁₋₄alkylsulfonyl,

carboxy,

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl,

10 (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)₀₋₂R⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴, O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl, (CH₂)_s-Z-(CH₂)_t-heteroaryl, (CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl,

15 (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with
 20 one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

25 each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, trifluoromethyl, C₁₋₄alkyl, and C₁₋₄alkoxy; or

30 two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

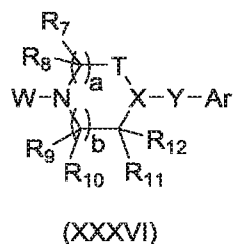
R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

35 R¹³ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy; and

each R¹⁴ is hydrogen or C₁₋₃alkyl.

Compounds of Formula (XXXV) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/089580. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/089580, the
 40 compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXVI:



5 or a pharmaceutically acceptable salt thereof; wherein

a is an integer selected from 0, 1, and 2;

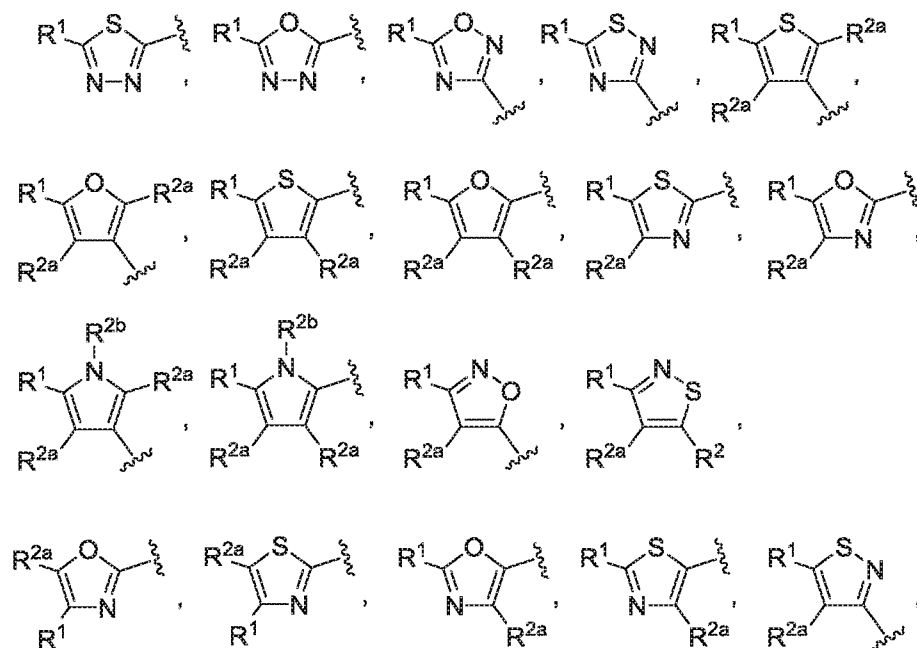
b is an integer selected from 0, 1, and 2;

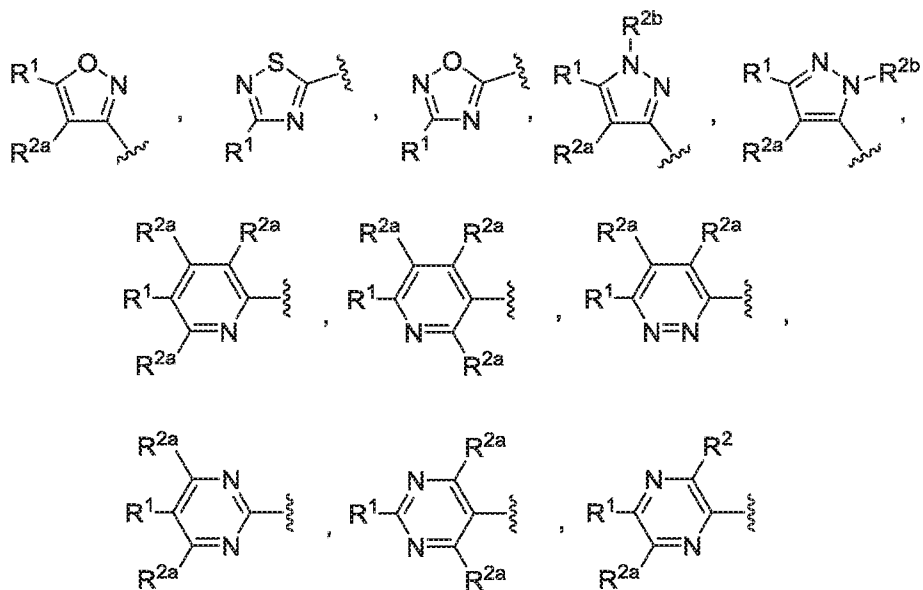
with the proviso that a and b cannot both be 2;

X-T is $N-CR^5R^6C=CR^5$ or $CR^{13}-CR^5R^6$;

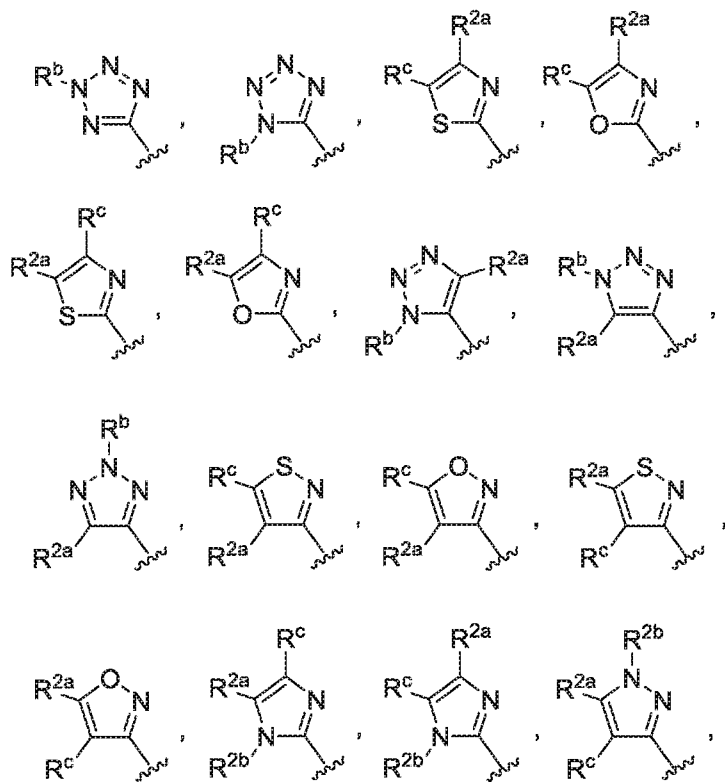
10 Y is a bond or $C(=O)$;

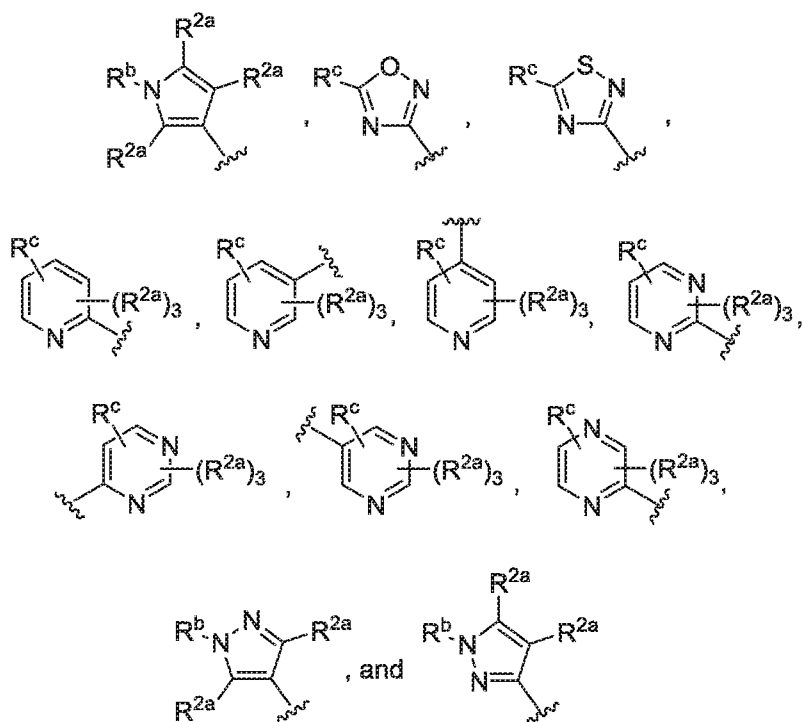
W is heteroaryl selected from the group consisting of:





R¹ is heteroaryl selected from the group consisting of:





wherein

R^b is $-(CH_2)_rCO_2H$, $-(CH_2)_rCO_2C_{1-3}alkyl$, $-(CH_2)_r-Z-(CH_2)_pCO_2H$, or $-(CH_2)_r-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

R^c is $-(CH_2)_mCO_2H$, $-(CH_2)_mCO_2C_{1-3}alkyl$, $-(CH_2)_m-Z-(CH_2)_pCO_2H$, or

5 $-(CH_2)_m-Z-(CH_2)_pCO_2C_{1-3}alkyl$;

Z is O, S, or NR^4 ;

each R^{2a} is independently selected from the group consisting of:

hydrogen,

halogen,

10 hydroxy,

cyano,

amino,

$C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkoxy$, optionally substituted with one to five fluorines,

15 $C_{1-4}alkylthio$, optionally substituted with one to five fluorines,

$C_{1-4}alkylsulfonyl$, optionally substituted with one to five fluorines, carboxy,

$C_{1-4}alkyloxycarbonyl$, and

$C_{1-4}alkylcarbonyl$;

each R^{2b} is independently selected from the group consisting of:

20 hydrogen,

$C_{1-4}alkyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkylsulfonyl$, optionally substituted with one to five fluorines,

$C_{1-4}alkyloxycarbonyl$, and

$C_{1-4}alkylcarbonyl$;

25 Ar is phenyl, naphthyl, thienyl, or pyridyl optionally substituted with one to five R^3 substituents;

each R^3 is independently selected from the group consisting of:

halogen,

cyano,

C₁₋₆alkyl, optionally substituted with one to five fluorines,

C₃₋₅cycloalkyl,

C₃₋₅cycloalkylmethyl, optionally substituted with C₁₋₃alkyl, C₁₋₆alkoxy, optionally substituted with one to five fluorines,

C₁₋₆alkylthio, optionally substituted with one to five fluorines, and

C₁₋₆alkylsulfonyl, optionally substituted with one to five fluorines;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl,

(CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, naphthyl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy;

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

or one of R⁵, R⁶, R⁷, and R⁸ together with one of R⁹, R¹⁰, R¹¹, and R¹² forms a direct bond or a C₁₋₂ alkylene bridge;

R¹³ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy;

m is an integer from 0 to 3;

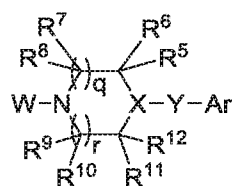
n is an integer from 0 to 2;

p is an integer from 1 to 3; and

r is an integer from 1 to 3.

Compounds of Formula (XXXVI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2010/094126. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2010/094126, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXVII:



(XXXVII)

or a pharmaceutically acceptable salt thereof; wherein

each m is independently an integer from 0 to 4;

each n is independently an integer from 0 to 2;

each s is independently an integer from 1 to 3;

each t is independently an integer from 1 to 3;

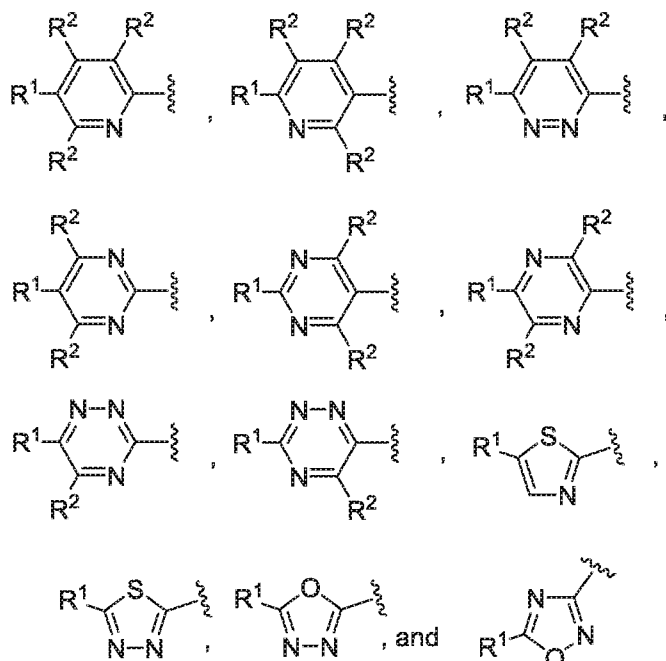
q is 0 or 1;

r is 0 or 1;

Z is O, S, or NR⁴;

X-Y is N-C(O), N-CR^aR^b, CR¹⁴-O, CR¹⁴-S(O)₀₋₂, or CR¹³-CR^aR^b;

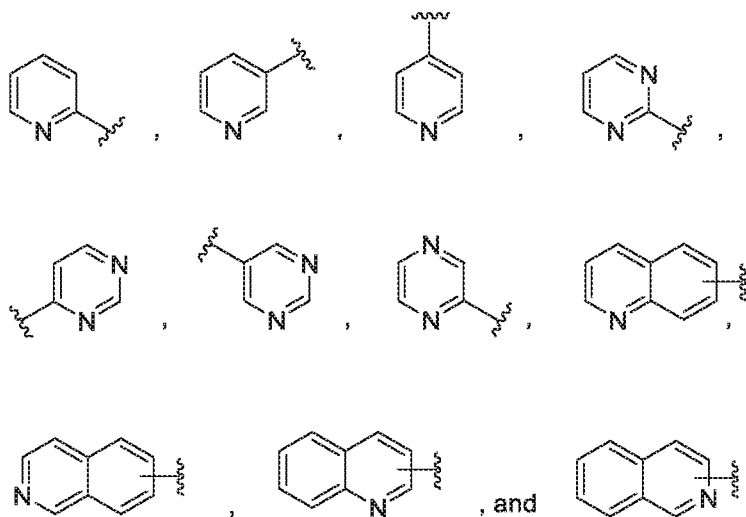
W is heteroaryl selected from the group consisting of:



5 Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R³ substituents;

R^a and R^b are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

R¹ is heteroaryl selected from the group consisting of:



10 wherein heteroaryl is monosubstituted with -(CH₂)_mCO₂H or -(CH₂)_mCO₂C₁₋₃alkyl and optionally substituted with one to three substituents independently selected from the group consisting of cyano, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylsulfonyl, and trifluoromethyl;

each R² is independently selected from the group consisting of:

hydrogen,

15 halogen,

hydroxy,

cyano,

ammo,

nitro,

C₁₋₄alkyl, optionally substituted with one to five fluorines,

C₁₋₄alkoxy, optionally substituted with one to five fluorines,

5 C₁₋₄alkylthio, optionally substituted with one to five fluorines,

C₁₋₄alkylsulfonyl,

carboxy,

C₁₋₄alkyloxycarbonyl, and

C₁₋₄alkylcarbonyl;

10 each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴, (CH₂)_nN(R⁴)₂, (CH₂)_nO=N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)₀₋₂R⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴, O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl,

15 (CH₂)_s-Z-(CH₂)_t-heteroaryl, (CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl, (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

20 in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form

25 a cyclopropyl group;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

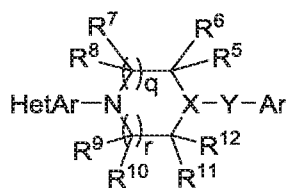
30

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

35 R¹³ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy; and each R¹⁴ is hydrogen or C₁₋₃alkyl.

Compounds of Formula (XXXVII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/046226. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/046226, the compounds of which are herein incorporated by reference.

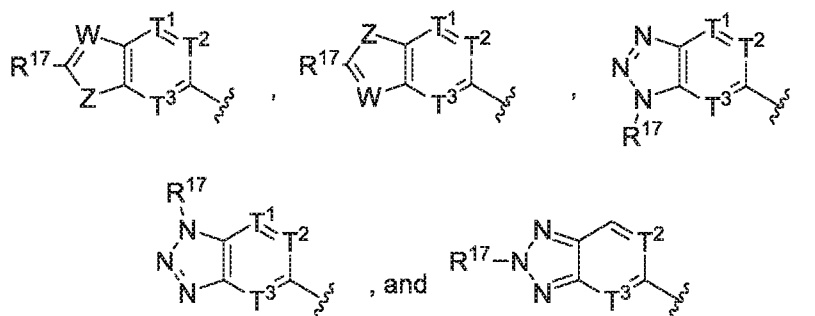
40 In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XXXVIII:



(XXXVIII)

or a pharmaceutically acceptable salt thereof; wherein

HetAr is a fused heteroaromatic ring selected from the group consisting of:



- 5 wherein W is N or CR¹⁶;
Z is O S or NR¹⁵;
T¹, T², and T³ are each independently N or CR¹⁶, with the proviso that at least one of T¹, T²,
and T³ is N;

- q is 0 or 1;
10 r is 0 or 1;
X-Y is N-C(O), CR¹⁴-O, CR¹⁴-S(O)₀₋₂, or CR¹³-CR¹R²;

Ar is phenyl, benzyl, naphthyl, or heteroaryl each of which is optionally substituted with one to five R³ substituents;

- R¹ and R² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with
15 one to three substituents independently selected from fluorine and hydroxyl;

- each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl, (CH₂)_n-phenyl,
(CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴,
(CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)₀₋₂R⁴,
(CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴,
20 O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl, (CH₂)_s-Z-(CH₂)_t-heteroaryl,
(CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl, (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂,
(CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂,
(CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂,
(CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃,
25 and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with
one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and
C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two
groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the

same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

Z is O, S, or NR⁴;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl,

5 (CH₂)_m-phenyl, (CH₂)_m-heteroaryl, (CH₂)_m-naphthyl, and (CH₂)_mC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

10 R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl,

wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

R¹³ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy;

each R¹⁴ is hydrogen or C₁₋₃alkyl;

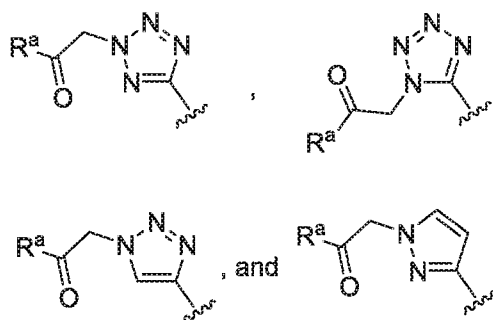
15 R¹⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkylcarbonyl,

aryl-C₁₋₂alkylcarbonyl, arylcarbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylsulfonyl, arylsulfonyl, aryl-C₁₋₂alkylsulfonyl, C₁₋₄alkyloxycarbonyl, aryloxycarbonyl, and aryl-C₁₋₂alkyloxycarbonyl;

R¹⁶ is hydrogen, amino, halogen, or C₁₋₃alkyl optionally substituted with one to five fluorines;

R¹⁷ is selected from the group consisting of: -(CH₂)_vC(O)R^a, -O(CH₂)_wC(O)R^a, -S(CH₂)_wC(O)R^a,

20 -NH(CH₂)_wC(O)R^a, -NCH₃(CH₂)_wC(O)R^a,



R^a is -OH, -OC₁₋₄alkyl, -NH₂, -NHSO₂C₁₋₄alkyl, -NHSO₂C₃₋₆cycloalkyl, or -NHSO₂CH₂C₃₋₆cycloalkyl;

each m is independently an integer from 0 to 2;

25 each n is independently an integer from 0 to 2;

each s is independently an integer from 1 to 3;

each t is independently an integer from 1 to 3;

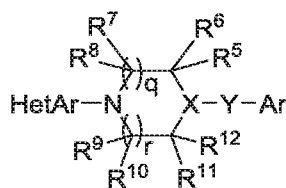
v is an integer from 1 to 3; and

each w is an integer from 1 to 2.

30 Compounds of Formula (XXXVIII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/012573. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/012573, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of

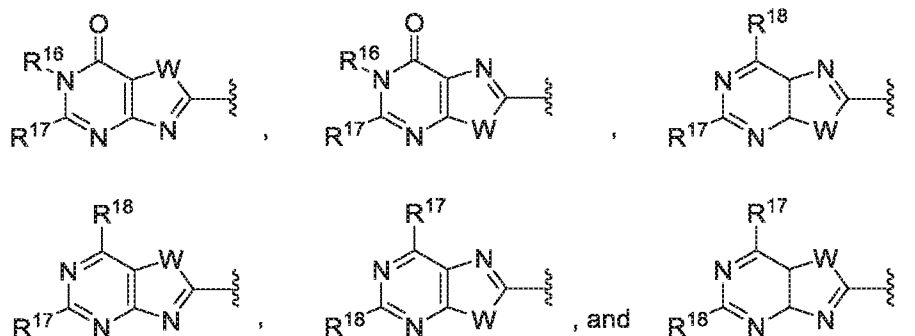
35 Formula XXXIX:



(XXXIX)

or a pharmaceutically acceptable salt thereof; wherein

HetAr is a fused heteroaromatic ring selected from the group consisting of:



- 5 q is 0 or 1;
r is 0 or 1;
W is O, S, or NR¹⁵;
X-Y is N-C(O), CR¹⁴-O, CR¹⁴-S(O)₀₋₂, or CR¹³-CR¹R²;
Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R³ substituents;
10 R¹ and R² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

- each R³ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₆alkenyl, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, nitro, (CH₂)_nOR⁴, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂,
15 (CH₂)_nS(O)₀₋₂R⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nC(O)R⁴, O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-phenyl, (CH₂)_s-Z-(CH₂)_t-naphthyl, (CH₂)_s-Z-(CH₂)_t-heteroaryl, (CH₂)_s-Z-(CH₂)_t-heterocyclyl, (CH₂)_s-Z-(CH₂)_t-C₃₋₇cycloalkyl, (CH₂)_s-Z-(CH₂)_t-OR⁴, (CH₂)_s-Z-(CH₂)_t-N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴SO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C≡N, (CH₂)_s-Z-(CH₂)_t-CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-SO₂N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-S(O)₀₋₂R⁴,
20 (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-C(O)N(R⁴)₂, (CH₂)_s-Z-(CH₂)_t-NR⁴C(O)R⁴, (CH₂)_s-Z-(CH₂)_t-NR⁴CO₂R⁴, (CH₂)_s-Z-(CH₂)_t-C(O)R⁴, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

- in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R₃ is optionally substituted with one to two
25 groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

Z is O, S, or NR⁴;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl,

$(\text{CH}_2)_m$ -phenyl, $(\text{CH}_2)_m$ -heteroaryl, $(\text{CH}_2)_m$ -naphthyl, and $(\text{CH}_2)_m\text{C}_{3-7}$ cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally

5 containing an additional heteroatom selected from O, S, NH, and NC $_{1-4}$ alkyl;

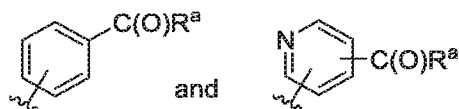
R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} are each independently hydrogen, fluorine, or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

R^{13} is hydrogen, C_{1-3} alkyl, fluorine, or hydroxy; each R^{14} is independently hydrogen or C_{1-3} alkyl;

10 R^{15} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, aryl- C_{1-2} alkylcarbonyl, arylcarbonyl, C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, arylsulfonyl, aryl- C_{1-2} alkylsulfonyl, C_{1-4} alkyloxycarbonyl, aryloxycarbonyl, and aryl- C_{1-2} alkyloxycarbonyl;

R^{16} is hydrogen or C_{1-3} alkyl optionally substituted with one to five fluorines;

15 R^{17} is selected from the group consisting of: $-(\text{CH}_2)_v\text{C}(\text{O})\text{R}^a$, $-(\text{CH}_2)_y\text{-T-(CH}_2)_z\text{C}(\text{O})\text{R}^a$, $-(\text{CH}_2)_y\text{-T-(CH}_2)_z\text{SO}_3\text{H}$, $-(\text{CH}_2)_y\text{-T-(CH}_2)_w$ -phenyl, $-(\text{CH}_2)_y\text{-T-(CH}_2)_w$ -heteroaryl,



wherein phenyl and heteroaryl are optionally substituted with one to two substituents independently selected from halogen, C_{1-4} alkyl, $-(\text{CH}_2)_x\text{C}(\text{O})\text{R}^a$, and $-\text{CH}=\text{CHC}(\text{O})\text{R}^a$;

wherein any methylene (CH_2) carbon atom in R^{17} is optionally substituted with one to two groups

20 independently selected from amino, carboxy, fluorine, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom

to which they are attached to form a cyclopropyl group;

T is O, S or NR^{14} ;

25 R^a is -OH, $-\text{OC}_{1-4}$ alkyl, $-\text{NH}_2$, $-\text{NHSO}_2\text{C}_{1-4}$ alkyl, $-\text{NHSO}_2\text{C}_{3-6}$ cycloalkyl, or $-\text{NHSO}_2\text{CH}_2\text{C}_{3-6}$ cycloalkyl;

30 R^{18} is selected from the group consisting of: amino, halogen, C_{1-4} alkoxy, optionally substituted with hydroxy or carboxy, C_{1-4} alkylthio, optionally substituted with hydroxy or carboxy, C_{1-4} alkylamino, di- $(\text{C}_{1-4}$ alkyl)amino, arylamino, aryl- C_{1-2} alkylamino, C_{1-4} alkylcarbonylamino, aryl- C_{1-2} alkylcarbonylamino, arylcarbonylamino, C_{1-4} alkylaminocarbonylamino, C_{1-4} alkylsulfonylamino, arylsulfonylamino, aryl- C_{1-2} alkylsulfonylamino, C_{1-4} alkyloxycarbonylamino, aryloxycarbonylamino, and aryl- C_{1-2} alkyloxycarbonylamino;

each m is independently an integer from 0 to 2;

each n is independently an integer from 0 to 2;

each s is independently an integer from 1 to 3;

35 each t is independently an integer from 1 to 3;

v is an integer from 0 to 4;

w is an integer from 0 to 2;

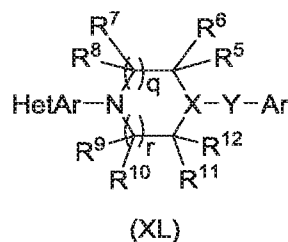
z is 1 or 2;

each x is an integer from 0 to 2; and

each y is 0 or 1.

Compounds of Formula (XXXIX) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/141455. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/141455, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XL:



or a pharmaceutically acceptable salt thereof; wherein each n is independently 0, 1 or 2;

q is 0 or 1;

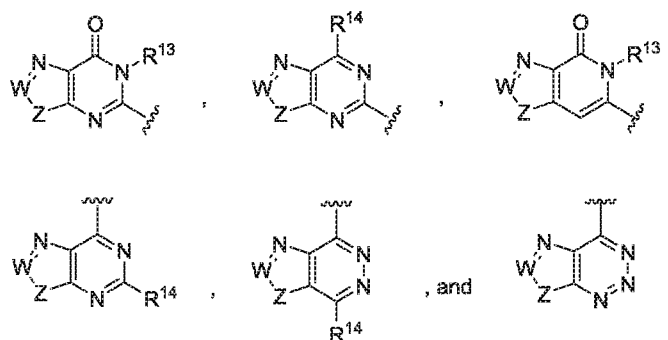
r is 0 or 1;

p is 0, 1, or 2;

X-Y is N-C(O), N-S(O)₂, N-CR¹R², CH-O, CH-S(O)_p, CH-NR¹³, or CR¹⁷-CR¹R²;

Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R³ substituents;

HetAr is a fused heteroaromatic ring selected from the group consisting of:



wherein Z is O, S, or N-R¹⁸;

W is N or C-R¹⁵;

R¹ and R² are each independently hydrogen, halogen, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; or R¹ and R² together with the carbon atom to which they are attached can form a spirocyclopropyl ring system;

each R³ is independently selected from the group consisting of: C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, OR⁴(CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the

same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups

together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl,

wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R¹³ is independently hydrogen or C₁₋₆alkyl;

R¹⁴ is independently selected from the group consisting of amino, hydroxy, mercapto, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylamino, di-(C₁₋₄alkyl)amino, arylamino, aryl-C₁₋₂alkylamino, C₁₋₄alkylcarbonylamino, aryl-C₁₋₂alkylcarbonylamino, arylcarbonylamino, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylsulfonylamino, arylsulfonylamino, aryl-C₁₋₂alkylsulfonylamino, C₁₋₄alkyloxycarbonylamino, aryloxycarbonylamino, and aryl-C₁₋₂alkyloxycarbonylamino;

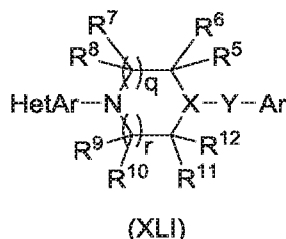
R¹⁵ and R¹⁶ are each independently hydrogen or C₁₋₄alkyl optionally substituted with amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyloxy, phenyl, heteroaryl, or one to five halogens;

R¹⁷ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy; and

R¹⁸ is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, aryl-C₁₋₂alkylcarbonyl, arylcarbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylsulfonyl, arylsulfonyl, aryl-C₁₋₂alkylsulfonyl, C₁₋₄alkyloxycarbonyl, aryloxycarbonyl, aryl-C₁₋₂alkyloxycarbonyl, β-D-ribofuranosyl, α-D-ribofuranosyl, β-D-glucopyranosyl, and α-D-glucopyranosyl.

Compounds of Formula (XL) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/017161. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/017161, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLI:



or a pharmaceutically acceptable salt thereof; wherein

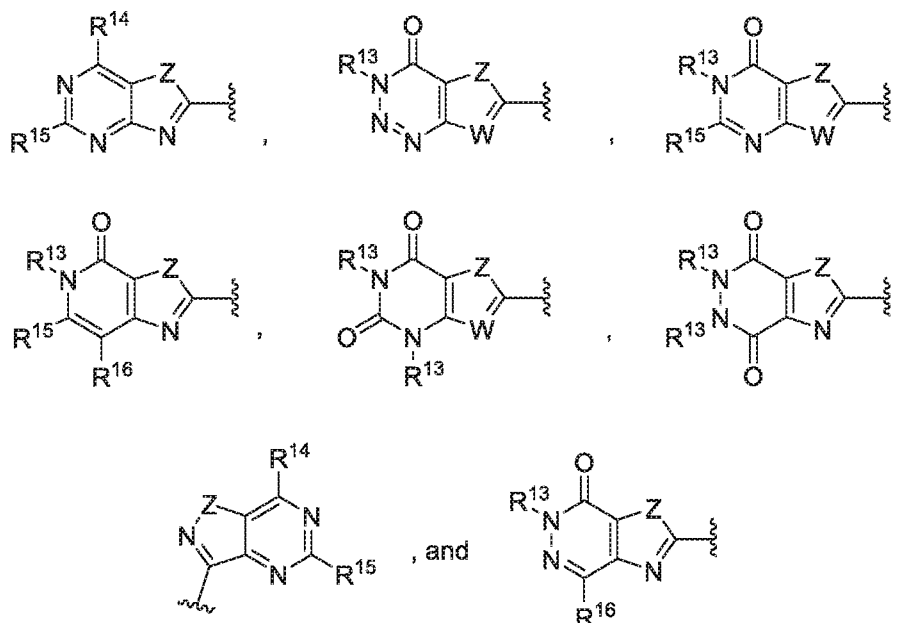
each n is independently 0, 1 or 2;

p is 0, 1, or 2;

X-Y is N-C(O), N-S(O)₂, N-CR¹R², CH-O, CH-S(O)_p, CH-N R¹³, CR¹⁷-CR¹R², or CH-C(O);

Ar is phenyl, naphthyl, or heteroaryl optionally substituted with one to five R³ substituents;

HetAr is a fused heteroaromatic ring selected from the group consisting of:



wherein Z is O, S, or N-R¹⁸;

- 5 R¹ and R² are each independently hydrogen, halogen, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; or R¹ and R² together with the carbon atom to which they are attached can form a spirocyclopropyl ring system; each R³ is independently selected from the group consisting of: C₁₋₆ alkyl, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, OR⁴, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

- in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkyl, trifluoromethyl, and C₁₋₄alkoxy; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

- each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄alkyl;

- 25 R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are each independently hydrogen, fluorine, or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R¹³ is independently hydrogen or C₁₋₆alkyl;

R¹⁴ is independently selected from the group consisting of amino, hydroxy, mercapto, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylamino, di-(C₁₋₄alkyl)amino, arylamino, aryl-C₁₋₂alkylamino, C₁₋₄alkylcarbonylamino, aryl-C₁₋₂alkylcarbonylamino, arylcarbonylamino, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylsulfonylamino, arylsulfonylamino, aryl-C₁₋₂alkylsulfonylamino, C₁₋₄alkyloxycarbonylamino, aryloxycarbonylamino, and aryl-C₁₋₂alkyloxycarbonylamino;

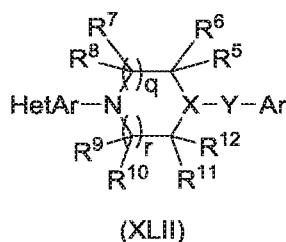
R¹⁵ and R¹⁶ are each independently hydrogen or C₁₋₄alkyl optionally substituted with amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyloxy, phenyl, heteroaryl, or one to five halogens;

R¹⁷ is hydrogen, C₁₋₃alkyl, fluorine, or hydroxy; and

R¹⁸ is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, aryl-C₁₋₂alkylcarbonyl, arylcarbonyl, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylsulfonyl, arylsulfonyl, aryl-C₁₋₂alkylsulfonyl, C₁₋₄alkyloxycarbonyl, aryloxycarbonyl, and aryl-C₁₋₂alkyloxycarbonyl.

Compounds of Formula (XLI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2007/056846. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2007/056846, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLII:



or a pharmaceutically acceptable salt thereof; wherein

each n is independently 0, 1 or 2;

each m is independently 0, 1, or 2;

each p is independently 0, 1, or 2;

X-Y is N-C(O), N-S(O)₂, N-CR¹R², CH-O, CH-S(O)_p, CH-NR¹³, CH-CR¹R², or CH-C(O);

Ar is phenyl, naphthyl, or heteroaryl each of which is optionally substituted with one to five R^{3a} substituents;

HetAr is an optionally fused five-membered heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, benzthiazolyl, benzoxazolyl, benzimidazolyl, benzisoxazolyl, and benzisothiazolyl;

in which the heteroaromatic ring is optionally substituted with one to two substituents independently selected from R^{3b};

R¹ and R² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy;

each R^{3a} and each R^{3b} is independently selected from the group consisting of: C_{1-6} alkyl, $(CH_2)_nOR^4$, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_nC_{3-7}$ cycloalkyl, halogen, $(CH_2)_nN(R^4)_2$, $(CH_2)_nC\equiv N$, $(CH_2)_nCO_2R^4$, $(CH_2)_nCOR^4$, NO_2 , $(CH_2)_nNR^4SO_2R^4$, $(CH_2)_nSO_2N(R^4)_2$, $(CH_2)_nS(O)_pR^4$, $(CH_2)_nNR^4C(O)N(R^4)_2$, $(CH_2)_nC(O)N(R^4)_2$, $(CH_2)_nC(O)N(OR^4)R^4$, $(CH_2)_nC(O)N(NH_2)R^4$, $(CH_2)_nNR^4C(O)R^4$, $(CH_2)_nNR^4CO_2R^4$, $O(CH_2)_nC(O)N(R^4)_2$, CF_3 , CH_2CF_3 , OCF_3 , and OCH_2CF_3 ;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkoxy, C_{3-6} cycloalkyl, and C_{1-4} alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH_2) carbon atom in R^{3a} or R^{3b} is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C_{1-4} alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R^4 is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, $(CH_2)_m$ -phenyl, $(CH_2)_m$ -heteroaryl, $(CH_2)_m$ -naphthyl, and $(CH_2)_mC_{3-7}$ cycloalkyl;

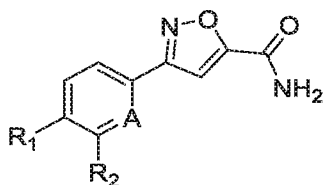
wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC $_{1-4}$ alkyl;

R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} are each independently hydrogen, fluorine, or C_{1-3} alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; and

R^{13} is hydrogen or C_{1-6} alkyl.

Compounds of Formula (XLII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2006/130986. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2006/130986, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLIII,



(XLIII)

wherein:

A is $-CH-$ or nitrogen;

R^1 is $-O-CH_2-R^3$, $-CH_2-O-R^3$ or $-CH_2-R^4$;

R^2 is hydrogen or halogen;

R^3 is $-phenyl$, optionally mono- or bi-substituted independently with lower alkyl, alkoxy, halogen,

-CN, -CF₃, -OCF₃, -SCF₃, -S(=O)CF₃ or -SO₂CH₃, or -pyridinyl, optionally substituted with lower alkyl or halogen; and

R⁴ is indolyl, dihydroindolyl, isoindolyl, dihydroisoindolyl, benzotriazolyl, benzoimidazolyl, indazolyl, tetrahydroquinolyl, methyldihydroindolyl or methylindolyl;

5 or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLIII, A is -CH-;

In some embodiments of the compound of Formula XLIII, R¹ is -O-CH₂-R³;

In some embodiments of the compound of Formula XLIII, R¹ is -CH₂-O-R³;

In some embodiments of the compound of Formula XLIII, R¹ is -CH₂-R⁴;

10 In some embodiments of the compound of Formula XLIII, R² is hydrogen or chlorine;

In some embodiments of the compound of Formula XLIII, R³ is phenyl, mono- or bi-substituted independently with lower alkyl, alkoxy, halogen, -CN, -CF₃, -OCF₃, -SCF₃, -S(=O)CF₃ or -SO₂CH₃;

15 In some embodiments of the compound of Formula XLIII, R³ is pyridinyl substituted with lower alkyl or halogen;

In some embodiments of the compound of Formula XLIII, R⁴ is indolyl, dihydroindolyl, isoindolyl, dihydroisoindolyl;

In some embodiments of the compound of Formula XLIII, R⁴ is benzotriazolyl, benzoimidazolyl, indazolyl, tetrahydroquinolyl, methyldihydroindolyl or methylindolyl;

20 In some embodiments, the compound of Formula XLIII is selected from:

3-[4-(2-Trifluoromethylsulfanyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Trifluoromethanesulfinyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Methoxy-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(3,4-Dimethyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

25 3-[4-(2-Cyano-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(3,4-Difluoro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Fluoro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Methyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

30 3-[4-(2-Trifluoromethoxy-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Iodo-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Chloro-5-fluoro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[5-(2-Chloro-benzyloxy)-pyridin-2-yl]-isoxazole-5-carboxylic acid amide;

35 3-[4-(2-Chloro-pyridin-3-ylmethoxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(3-Fluoro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(3-Trifluoromethyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(3-Chloro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Chloro-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

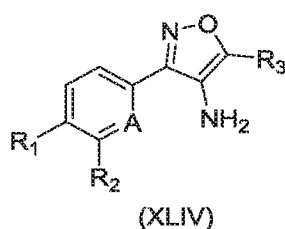
40 3-[4-(2-Bromo-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Trifluoromethyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;

3-[4-(2-Methanesulfonyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-(4-o-Tolyloxymethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-(4-m-Tolyloxymethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Methoxy-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 5 3-[4-(3-Methoxy-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(4-Methoxy-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2,6-Dimethyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Isopropyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Trifluoromethoxy-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 10 3-[4-(2-Ethyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-tert-Butyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Trifluoromethyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Cyano-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(3-Methyl-pyridin-2-yloxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 15 3-[4-(2-Fluoro-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(5-Chloro-2-methyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(3-Chloro-2-methyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(4-Fluoro-2-methyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(5-Fluoro-2-methyl-phenoxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 20 3-[4-(2-Methyl-pyridin-3-yloxy-methyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2,3-Dihydro-indol-1-ylmethyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(1,3-Dihydro-isindol-2-ylmethyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-(4-Indol-1-ylmethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-(4-Benzotriazol-1-ylmethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 25 3-(4-Benzimidazol-1-ylmethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-(4-Indazol-1-ylmethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-(4-Indazol-2-ylmethyl-phenyl)-isoxazole-5-carboxylic acid amide;
 3-[4-(3,4-Dihydro-2H-quinolin-1-ylmethyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 3-[4-(2-Methyl-2,3-dihydro-indol-1-ylmethyl)-phenyl]-isoxazole-5-carboxylic acid amide;
 30 3-[4-(4-Methyl-indol-1-ylmethyl)-phenyl]-isoxazole-5-carboxylic acid amide; or
 3-[3-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenyl]-isoxazole-5-carboxylic acid amide.

Compounds of Formula (XLIII) may be synthesized by methods known in the art, e.g., those described in U.S. Patent No. 9,296,711 B2. In some embodiments, the SCD inhibitor is a compound disclosed in U.S. Patent No. 9,296,711 B2, the compounds of which are herein incorporated by reference.

35 In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLIV,



wherein:

A is -CH- or nitrogen;

R¹ is -O(CH₂)_nR⁴, -CH₂NHR⁴, -CH₂CH₂R⁴, -OCH₂C(O)R⁴ or -CH₂OR⁴;

R² is hydrogen or halogen;

5 R³ is hydrogen or lower alkyl;

R⁴ is phenyl, pyridinyl, 1,1-dioxo-2,3-dihydro-1H-1λ⁶-benzo[b]thiophenyl or 1,1-dioxo-1H-1λ⁶-benzo[b]thiophenyl, said phenyl optionally mono- or bi-substituted independently with halogen, lower alkyl, alkoxy, -C(O)OCH₃, -S(O)₂CH₃, -NO₂, -CN, -CF₃, -OCF₃, -SCH₃, -SO₂-phenyl, -SCF₃ or -SO₂CH₂CH₃; and

10 n is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLIV, A is -CH-;

In some embodiments of the compound of Formula XLIV, R¹ is -O(CH₂)_nR⁴ or -CH₂NHR⁴;

In some embodiments of the compound of Formula XLIV, R¹ is -O(CH₂)_nR⁴;

15 In some embodiments of the compound of Formula XLIV, R¹ is -OCH₂R⁴;

In some embodiments of the compound of Formula XLIV, R² is hydrogen;

In some embodiments of the compound of Formula XLIV, R³ is hydrogen or methyl;

In some embodiments of the compound of Formula XLIV, R⁴ is unsubstituted phenyl, pyridinyl, 1,1-dioxo-2,3-dihydro-1H-1λ⁶-benzo[b]thiophenyl or 1,1-dioxo-1H-1λ⁶-

20 benzo[b]thiophenyl;

In some embodiments of the compound of Formula XLIV, R⁴ is unsubstituted phenyl;

In some embodiments of the compound of Formula XLIV, R⁴ is phenyl mono-substituted with Cl, F, I, methyl, isopropyl, -OCH₃, -C(O)OCH₃, S(O)₂CH₃, -NO₂, -CN, CF₃, -OCF₃, -SCH₃, -SO₂-phenyl, -SCF₃ or -SO₂CH₂CH₃;

25 In some embodiments of the compound of Formula XLIV, R⁴ is phenyl bi-substituted independently with methyl or halogen;

In some embodiments, the compound of Formula XLIII is selected from:

3-[4-(4-Fluoro-benzyloxy)-phenyl]-isoxazol-4-ylamine;

3-(4-Benzyloxy-phenyl)-isoxazol-4-ylamine;

30 3-[4-(4-Methoxy-benzyloxy)-phenyl]-isoxazol-4-ylamine;

4-[4-(4-Amino-isoxazol-3-yl)-phenoxy-methyl]-benzoic acid methyl ester hydrochloride;

3-[4-(4-Methanesulfonyl-benzyloxy)-phenyl]-isoxazol-4-ylamine;

3-{4-[(4-methanesulfonyl-phenylamino)-methyl]-phenyl}-isoxazol-4-ylamine hydrochloride;

3-[4-(2-Chloro-4-methanesulfonyl-benzyloxy)-phenyl]-isoxazol-4-ylamine;

35 3-{4-[2-(4-Methanesulfonyl-phenyl)-ethyl]-phenyl}-isoxazol-4-ylamine;

3-(5-Phenethyloxy-pyridin-2-yl)-isoxazol-4-ylamine;

3-[4-(3-Phenyl-propoxy)-phenyl]-isoxazol-4-ylamine;

3-[5-(4-Methanesulfonyl-benzyloxy)-pyridin-2-yl]-isoxazol-4-ylamine;

3-[4-(4-Methanesulfonyl-benzyloxy)-phenyl]-5-methyl-isoxazol-4-ylamine;

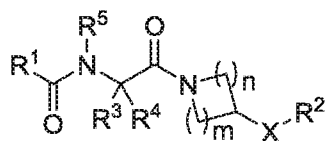
40 3-[4-(Pyridin-3-ylmethoxy)-phenyl]-isoxazol-4-ylamine;

2-[4-(4-Amino-isoxazol-3-yl)-phenoxy]-1-phenyl-ethanone hydrochloride;

- 3-[4-(4-Nitro-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 4-[4-(4-Amino-isoxazol-3-yl)-phenoxy-methyl]-benzonitrile hydrochloride;
 3-[4-(4-Amino-isoxazol-3-yl)-phenoxy-methyl]-benzonitrile hydrochloride;
 3-[4-(4-Trifluoromethyl-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(4-Trifluoromethoxy-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(3,5-Difluoro-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(2-Chloro-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(3,4-Dimethyl-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(3-Trifluoromethoxy-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(4-Chloro-benzyloxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(3, 4-Dichloro-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(4-Methyl-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(4-Iodo-benzyloxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(4-Isopropyl-benzyloxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(4-Methanesulfonyl-benzyloxy)-phenyl]-isoxazol-4-ylamine hydrochloride;
 3-[4-(4-Ethanesulfonyl-benzyloxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(1,1-Dioxo-2,3-dihydro-1H-1lambda*6*-benzo[b]thiophen-5-ylmethoxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(1,1-Dioxo-1H-1lambda*6*-benzo[b]thiophen-5-yl-methoxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(4-Benzenesulfonyl-benzyloxy)-phenyl]-isoxazol-4-ylamine;
 3-[4-(4-Methylsulfanyl-benzyloxy)-phenyl]-isoxazol-4-ylamine; and
 3-[4-(4-Trifluoromethylsulfanyl-benzyloxy)-phenyl]-isoxazol-4-ylamine.

Compounds of Formula (XLIV) may be synthesized by methods known in the art, e.g., those described in U.S. Patent No. 9,290,465 B2. In some embodiments, the SCD inhibitor is a compound disclosed in U.S. Patent No. 9,290,465 B2, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLV,



(XLV)

wherein

R¹ is aryl or heteroaryl;

R² is aryl or heteroaryl;

R³ and R⁴ are each independently hydrogen, halogen or alkyl; or

R³ and R⁴, together with the carbon atom to which they are attached, form a cycloalkyl group;

R⁵ is hydrogen or alkyl;

m and n are, independently, 1 or 2;

X is -O-, -NR⁶-, -S-, -S(O)- or -S(O)₂- where R⁶ is hydrogen or alkyl;

wherein, when present, an aryl, heteroaryl or heterocycle group may optionally be substituted by one or more halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and combinations thereof;

or pharmaceutically acceptable salts, solvates, hydrates, solvates of pharmaceutically acceptable salts thereof, or enantiomer or diastereomer thereof;

with the proviso that said compound is not

4-[(2R)-2,3-dihydro-2-methyl-6-nitroimidazo[2,1-b]oxazol-2-yl]methoxy-N-[2-oxo-2-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]ethyl]-benzamide,

N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-M-methylbenzamide,

4-amino-N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-benzamide,

or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, R¹ is aryl or heteroaryl;

R² is aryl or heteroaryl;

R³ and R⁴ are each independently hydrogen, halogen or alkyl; or

R³ and R⁴, together with the carbon atom to which they are attached, form a cycloalkyl group;

R⁵ is hydrogen or alkyl;

m and n are, independently, 1 or 2;

X is -O-, -NR⁶-, -S-, -S(O)- or -S(O)₂- where R⁶ is hydrogen or alkyl;

wherein, when present, an aryl or heteroaryl group may optionally be substituted by one or more halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and combinations thereof;

or pharmaceutically acceptable salts, or enantiomer or diastereomer thereof;

with the proviso that said compound is not

4-[(2R)-2,3-dihydro-2-methyl-6-nitroimidazo[2,1-b]oxazol-2-yl]methoxy-N-[2-oxo-2-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]ethyl]-benzamide,

N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-M-methylbenzamide,

4-amino-N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-benzamide,

or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, R¹ is aryl that is substituted by one or more aryl groups.

In some embodiments of the compound of Formula XLV, R¹ is heteroaryl and is substituted by one or more aryl or heteroaryl groups.

5 In some embodiments of the compound of Formula XLV, R¹ is pyrazole, triazole, or isoxazole.

In some embodiments of the compound of Formula XLV, R² is aryl.

In some embodiments, the compound of Formula XLV is selected from:

1-Cyclopentyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide;

10 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-cyano-2-methyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide;

1-Morpholin-4-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide;

15 1-Morpholin-4-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide;

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(2,5-difluoro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide;

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide; and

20 1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

Biphenyl-4-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

25 Biphenyl-4-carboxylic acid {2-[4-(2-bromo-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

Biphenyl-4-carboxylic acid {2-[4-(2-bromo-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

Biphenyl-4-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

Biphenyl-4-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenylamino)-piperidin-1-yl]-ethyl}-amide,

30 Biphenyl-4-carboxylic acid {2-[4-[methyl-(2-trifluoromethyl-phenyl)-amino]-piperidin-1-yl]-2-oxo-ethyl}-amide,

Biphenyl-4-carboxylic acid {2-[4-[(2-chloro-phenyl)-methyl-amino]-piperidin-1-yl]-2-oxo-ethyl}-amide,

35 Biphenyl-4-carboxylic acid {2-[4-[(2-bromo-phenyl)-methyl-amino]-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-isoxazole-3-carboxylic acid {2-[4-(2-bromo-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-isoxazole-3-carboxylic acid {2-[4-(2-bromo-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

40 5-Phenyl-isoxazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-isoxazole-3-carboxylic acid (2-{4-[(2-bromo-phenyl)-methyl-amino]-piperidin-1-yl}-2-oxo-ethyl)-amide,

5-Phenyl-isoxazole-3-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenylamino)-piperidin-1-yl]-ethyl}-amide,

5 5-Phenyl-isoxazole-3-carboxylic acid (2-{4-[methyl-(2-trifluoromethyl-phenyl)-amino]-piperidin-1-yl}-2-oxo-ethyl)-amide,

N-{2-oxo-2-[4-(2-trifluoromethyl-phenylamino)-piperidin-1-yl]-ethyl}-4-phenylamino-benzamide,

N-{2-[4-(2-Chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-4-phenylamino-benzamide

N-{2-[4-(2-Bromo-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-4-phenylamino-benzamide

10 N-(2-{4-[Methyl-(2-trifluoromethyl-phenyl)-amino]-piperidin-1-yl}-2-oxo-ethyl)-4-phenylamino-benzamide,

N-{2-[4-(2-Bromo-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-4-phenylamino-benzamide

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-bromo-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}

15 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-bromo-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}

20 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenylsulfanyl)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chlorophenylsulfanyl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-nitro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-amino-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-

25 amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2,3-dimethyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide, and

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2,4-dimethyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

30 or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2,5-dimethyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}

35 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-tert-butyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-bromo-phenylsulfanyl)-piperidin-1-yl]-2-oxo-ethyl}

5-Phenyl-1H-pyrazole-3-carboxylic acid [2-oxo-2-(4-o-tolylamino-piperidin-1-yl)-ethyl]-amide,

40 5-(3-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-pyridine-2-carboxylic acid {2-oxo-2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-pyridine-2-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(4-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5 5-(2-Hydroxy-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

Synthesis of 5-(2-Hydroxy-phenyl)-isoxazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

10 5-(2-Hydroxy-phenyl)-isoxazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

15 N-{2-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-6-phenylamino-nicotinamide,

N-{2-[4-(2-Chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-6-phenylamino-nicotinamide,

5-Phenylamino-pyridine-2-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

20 5-Phenylamino-pyridine-2-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(5-bromo-2-methoxy-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

25 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-cyano-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

30 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2,4-difluoro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(5-fluoro-2-trifluoromethyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

35 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-acetyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(5-cyano-2-methyl-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

40 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-benzenesulfinyl)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(pyridin-4-yloxy)-piperidin-1-yl]-ethyl}-amide,
and

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5 or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-hydroxy-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-benzenesulfonyl)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(6-chloro-pyridin-2-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

4-Methyl-3-(1-{2-[(5-phenyl-1H-pyrazole-3-carbonyl)-amino]-acetyl}-piperidin-4-yloxy)-benzoic acid methyl ester,

15 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-fluoro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

20 5-(2-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(4-Trifluoromethyl-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(3-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

25 5-(3-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Trifluoromethyl-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

30 5-(4-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(3-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(4-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

35 5-(4-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(4-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

40 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(3-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

3-(1-{2-[(5-Phenyl-1H-pyrazole-3-carbonyl)-amino]-acetyl}-piperidin-4-yloxy)-benzoic acid,

5-(3-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid [2-oxo-2-(4-m-tolyloxy-piperidin-1-yl)-ethyl]-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-methyl-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Pyridin-2-yl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

3-(5-{2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethylcarbamoyl}-1H-pyrazol-3-yl)-benzoic acid,

5-Pyridin-3-yl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-Pyridin-3-yl-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(4-methyl-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(5-trifluoromethyl-pyridin-3-yloxy)-piperidin-1-yl]-ethyl}-amide,

5-(5-Chloro-thiophen-2-yl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(5-Chloro-thiophen-2-yl)-1H-pyrazole-3-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide, and

5-(2-Hydroxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-methanesulfonyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(2-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(2-Hydroxy-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(3-Hydroxy-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(4-Hydroxy-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(3-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(4-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-(4-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5 5-(4-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-[4-(2-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(3-Fluoro-phenyl)-isoxazole-3-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

10 1-Phenyl-1H-pyrazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

2-[(Biphenyl-4-ylmethyl)-amino]-1-[4-(2-chloro-phenoxy)-piperidin-1-yl]-ethanone,

N-{2-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-4-[1,3,4]oxadiazol-2-yl-benzamide,

4-Phenyl-pyrazole-1-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

15 1-Phenyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-(3-Fluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

20 1-(3-Fluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide

1-m-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

25 1-m-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-(2-Cyano-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-(2-Cyano-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

30 1-o-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

35 1-Cyclopentyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-(5-Fluoro-pyridin-3-yl)-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

N-{2-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzamide, and

40 3'-Dimethylamino-biphenyl-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

N-{2-Oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-4-(pyrrolidine-1-carbonyl)-benzamide,

5 9H-Carbazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-formyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

2-(1-{2-[(5-Phenyl-1H-pyrazole-3-carbonyl)-amino]-acetyl}-piperidin-4-yloxy)-benzoic acid,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-hydroxymethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid (2-{4-[2-(hydroxyimino-methyl)-phenoxy]-piperidin-1-yl}-2-oxo-ethyl)-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(3-cyano-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid (2-{4-[2-(methoxyimino-methyl)-phenoxy]-piperidin-1-yl}-2-oxo-ethyl)-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-methylcarbamoyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(2-carbamoyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Trifluoromethyl-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(3-cyano-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(adamantan-2-ylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-(2-Methoxy-phenyl)-1H-pyrazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyrrolidin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-(1-Methyl-pyrrolidin-3-yl)-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

1-(3,5-Difluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-(3,5-Difluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-chloro-pyridin-3-yloxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5 1-Piperidin-4-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide hydrochloride,

1-(1-Methyl-piperidin-4-yl)-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

10 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-cyano-2-methyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[3-(3-trifluoromethyl-phenoxy)-pyrrolidin-1-yl]-ethyl}-amide,

15 4-(2-Oxo-pyrrolidin-1-yl)-N-{2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-benzamide,

1-Cyclopropyl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide, and

20 1-Morpholin-4-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV is selected from:

1-Phenyl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(3-cyano-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

25 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(2,5-difluoro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[3-(3-trifluoromethyl-phenoxy)-azetidin-1-yl]-ethyl}-amide,

30 5-Pyridin-3-yl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[3-(3-trifluoromethyl-phenoxy)-azetidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[3-(2,5-difluoro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

35 1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(5-cyano-2-methyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

40 1-Phenyl-1H-imidazole-4-carboxylic acid {2-[3-(3-fluoro-5-trifluoromethyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(3-fluoro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

5 1-Phenyl-1H-imidazole-4-carboxylic acid {2-[3-(2-chloro-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[3-(5-cyano-2-methyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

10 1-Phenyl-1H-imidazole-4-carboxylic acid {2-[3-(2-chloro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide,

5-Phenyl-isoxazole-3-carboxylic acid {2-[3-(2,5-difluoro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide,

2-Phenyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid {2-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

15 6-Pyrazol-1-yl-imidazo[1,2-a]pyridine-2-carboxylic acid {2-[4-(2-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(3-cyano-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

20 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(3-fluoro-5-trifluoromethyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(3-fluoro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(2-chloro-phenoxy)-pyrrolidin-1-yl]-2-oxo-ethyl}-amide,

25 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(2-chloro-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

30 1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[3-(5-cyano-2-methyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-oxo-2-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl}-amide,

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[3-(3-fluoro-5-trifluoromethyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

35 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(3-fluoro-5-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

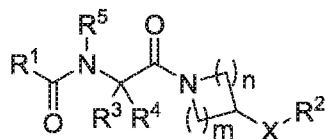
5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-amide,

40 5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[3-(2-chloro-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide, and

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-[3-(5-cyano-2-methyl-phenoxy)-azetidin-1-yl]-2-oxo-ethyl}-amide,

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula XLV has the structure:



wherein

R¹ is heteroaryl;

R² is aryl or heteroaryl;

R³ and R⁴ are each independently hydrogen, halogen or alkyl; or

R³ and R⁴, together with the carbon atom to which they are attached, form a cycloalkyl group;

R⁵ is hydrogen or alkyl;

m and n are, independently, 1 or 2;

X is -O-, -NR⁶-, -S-, -S(O)- or -S(O)₂- where R⁶ is hydrogen or alkyl;

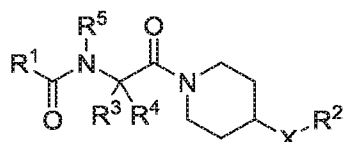
wherein, when present, an aryl or heteroaryl group may optionally be substituted by one or more

halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkoxycarbonyl,

aryloxycarbonyl or heteroaryloxycarbonyl, and combinations thereof;

or pharmaceutically acceptable salts or enantiomer or diastereomer thereof.

In some embodiments, the compound of Formula XLV has the structure:



wherein

R¹ is aryl or heteroaryl;

R² is aryl or heteroaryl;

R³ and R⁴ are each independently hydrogen, halogen or alkyl; or

R³ and R⁴, together with the carbon atom to which they are attached, form a cycloalkyl group;

R⁵ is hydrogen or alkyl;

X is -O-, -NR⁶-, -S-, -S(O)- or -S(O)₂- where R⁶ is hydrogen or alkyl;

wherein, when present, an aryl or heteroaryl group may optionally be substituted by one or more

halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkylthio, arylthio, alkylsulfinyl,

alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and combinations thereof;

and pharmaceutically acceptable salts thereof;

with the proviso that said compound is not

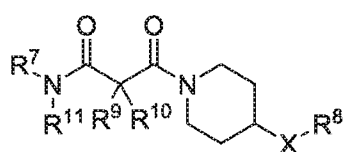
4-[[[(2R)-2,3-dihydro-2-methyl-6-nitroimidazo[2,1-b]oxazol-2-yl]methoxy]-N-[2-oxo-2-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]ethyl]-benzamide,

N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-M-methylbenzamide,

4-amino-N-[2-[4-[[4-amino-5-(2,6-difluorobenzoyl)-2-thiazolyl]amino]-1-piperidinyl]-2-oxoethyl]-benzamide,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula XLV has the structure:



wherein

R⁷ is aryl or heteroaryl;

R⁸ is aryl or heteroaryl;

R⁹ and R¹⁰ are each independently hydrogen, halogen or alkyl; or

R⁹ and R¹⁰, together with the carbon atom to which they are attached, form a cycloalkyl group;

R¹¹ is hydrogen or alkyl;

X is -O-, -NR¹²-, -S-, -S(O)- or -S(O)₂- where R¹² is hydrogen or alkyl;

wherein, when present, an aryl or heteroaryl group may optionally be substituted by one or more halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and combinations thereof.

In some embodiments, of the compound of Formula XLV is selected from:

N-Biphenyl-4-yl-3-[4-(2-bromo-phenoxy)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2-chloro-5-fluoro-phenoxy)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2-bromo-phenylamino)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2-bromo-phenylsulfanyl)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-oxo-3-(4-o-tolylamino-piperidin-1-yl)-propionamide,

N-Biphenyl-4-yl-3-[4-(2-nitro-phenoxy)-piperidin-1-yl]-3-oxo-propionamide,

3-[4-(2-Amino-phenoxy)-piperidin-1-yl]-N-biphenyl-4-yl-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2,3-dimethyl-phenylamino)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2,4-dimethyl-phenylamino)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2,5-dimethyl-phenylamino)-piperidin-1-yl]-3-oxo-propionamide,

N-Biphenyl-4-yl-3-[4-(2-tert-butyl-phenylamino)-piperidin-1-yl]-3-oxo-propionamide,
 N-Biphenyl-4-yl-3-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-3-oxo-propionamide,
 3-[4-(2-Chloro-5-fluoro-phenoxy)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-[4-(2-Chloro-5-fluoro-phenoxy)-piperidin-1-yl]-3-oxo-N-(5-phenyl-pyridin-2-yl)-propionamide,
 3-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-[4-(2-Chloro-phenylamino)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-[4-(2-Bromo-phenylamino)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-Oxo-N-(6-phenyl-pyridin-3-yl)-3-[4-(2-trifluoromethyl-phenylamino)-piperidin-1-yl]-propionamide,
 3-[4-(2-Chloro-phenylsulfanyl)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-[4-(2-Bromo-phenylsulfanyl)-piperidin-1-yl]-3-oxo-N-(6-phenyl-pyridin-3-yl)-propionamide,
 3-Oxo-N-(6-phenyl-pyridin-3-yl)-3-[4-(2-trifluoromethyl-phenylsulfanyl)-piperidin-1-yl]-
 propionamide,
 3-Oxo-N-(6-phenyl-pyridin-3-yl)-3-[4-(2-trifluoromethyl-phenoxy)-piperidin-1-yl]-propionamide,
 3-Oxo-N-(6-phenyl-pyridin-3-yl)-3-(4-o-tolylamino-piperidin-1-yl)-propionamide,
 3-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-3-oxo-N-(3-phenyl-[1,2,4]thiadiazol-5-yl)-propionamide,
 3-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-N-(4-[1,2,4]oxadiazol-3-yl-phenyl)-3-oxo-propionamide,
 3-[4-(2-Chloro-phenoxy)-piperidin-1-yl]-3-oxo-N-(5-phenyl-thiazol-2-yl)-propionamide,
 3-[4-(2-Chloro-phenylamino)-piperidin-1-yl]-3-oxo-N-(5-phenyl-thiazol-2-yl)-propionamide,
 1-[4-(2-Chloro-phenoxy)-piperidine-1-carbonyl]-cyclopropane carboxylic acid biphenyl-4-ylamide,
 N-Biphenyl-4-yl-3-oxo-3-[4-(3,4,5-trifluoro-phenoxy)-piperidin-1-yl]-propionamide, and
 N-Biphenyl-4-yl-3-[4-(3-cyano-phenoxy)-piperidin-1-yl]-3-oxo-propionamide,
 and pharmaceutically acceptable salts thereof.

In some embodiments of the compound of Formula XLV, the compound is:

Biphenyl-4-carboxylic acid {2-[4-[methyl-(2-trifluoromethyl-phenyl)-amino]-piperidin-1-yl]-2-oxo-
 ethyl}-amide or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, the compound is:

5-Phenyl-isoxazole-3-carboxylic acid {2-[4-(2-chloro-phenylamino)-piperidin-1-yl]-2-oxo-ethyl}-
 amide or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, the compound is:

5-Phenyl-1H-pyrazole-3-carboxylic acid {2-oxo-2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-
 ethyl}-amide or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, the compound is:

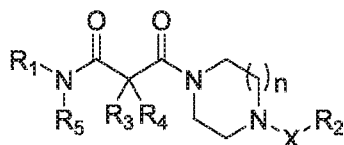
1-Pyridin-3-yl-1H-[1,2,3]triazole-4-carboxylic acid {2-[4-(5-cyano-2-methyl-phenoxy)-piperidin-1-
 yl]-2-oxo-ethyl}-amide or a pharmaceutically acceptable salt thereof.

In some embodiments of the compound of Formula XLV, the compound is:

1-Phenyl-1H-imidazole-4-carboxylic acid {2-[4-(2,5-difluoro-phenoxy)-piperidin-1-yl]-2-oxo-ethyl}-
 amide or a pharmaceutically acceptable salt thereof.

Compounds of Formula (XLV) may be synthesized by methods known in the art, e.g., those
 described in U.S. Patent No. 8,129,376 B2. In some embodiments, the SCD inhibitor is a compound
 disclosed in U.S. Patent No. 8,129,376 B2, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLVI,



wherein

n is 1 or 2;

R¹ is aryl, heterocycloalkane, heteroaryl or heterocycle;

R² is aryl, heteroaryl or heterocycle;

R³ and R⁴ are each independently hydrogen, halogen or alkyl; or

R³ and R⁴, together with the carbon atom to which they are attached, form a cycloalkyl group;

R⁵ is hydrogen or alkyl;

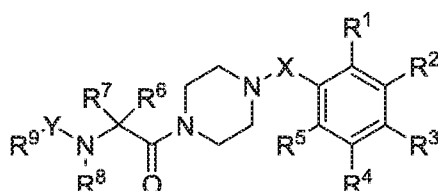
wherein when n is 1, then X is -C(O)-, -S(O)₂-, or -S(O)-, and when n is 2, then X is -C(O)-, -S(O)₂-, -S(O)- or -CR⁶R⁷- where R⁶ and R⁷ are each independently hydrogen or alkyl;

wherein, when present, an aryl, heteroaryl or heterocycle group may optionally be substituted by one or more halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, alkylamido, -O-C(O)-NH-, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkythio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkoxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, and combinations thereof;

and pharmaceutically acceptable salts, solvates, hydrates, or solvates of pharmaceutically acceptable salts thereof.

Compounds of Formula (XLVI) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/117659. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/117659, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLVII,



(XLVII)

wherein

R¹ is halogenated alkyl (e.g., CF₃);

R², R³, R⁴ and R⁵ are each independently hydrogen, halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, carboxyl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, cycloalkyloxy,

cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkythio, arylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, carbonyl, aryloxy, carbonyl or heteroaryloxy, carbonyl;

R^6 and R^7 are each independently hydrogen, hydroxyl, cyano, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl;

5 R^8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl;

R^9 is hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl;

10 X is $-C(O)-$, $-C(O)-O-$, $-S(O)_2-$, $-S(O)-$, or $-C(O)NR^{10}-$, where R^{10} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl;

Y is $-C(O)-$, $-S(O)_2-$, or $-S(O)-$;

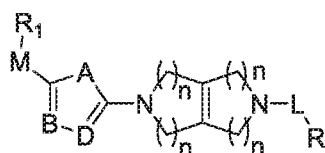
15 wherein, when present, any aryl, heteroaryl, or heterocycle group may optionally be substituted by halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, arylamino, diarylamino, amido, carboxyl, alkyl, halogenated alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, aroyl, acyl, alkoxy, aryloxy, heteroaryloxy, cycloalkyloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkythio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkoxy, carbonyl, aryloxy, carbonyl, heteroaryloxy, carbonyl, arylalkyl- $C(O)-$, $-C(O)O$ -alkyl, benzodioxol, benzo[d]oxazol-2(3H)-one, cycloalkyl-
20 $NH-C(O)-$, and combinations thereof;

or pharmaceutically acceptable salts or solvates (e.g., hydrates) or N-oxides thereof, or solvates of pharmaceutically acceptable salts thereof, or pharmaceutically acceptable salts or solvates of N-oxides thereof; or prodrugs thereof;

25 with the proviso that said compound is not 4-chloro-N-[2-oxo-2-[4-[[2-(trifluoromethyl)phenyl]sulfonyl]-1-piperazinyl]ethyl]benzamide or a pharmaceutically acceptable salt thereof.

30 Compounds of Formula (XLVII) may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/157844. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/157844, the compounds of which are herein incorporated by reference.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula XLVIII,



(XLVIII)

35 R is hydrogen, (C₁-C₁₆)-alkyl, (C₁-C₅)-alkyloxy, (C₁-C₅)-alkylthio, (C₁-C₅)-alkylamino, di-(C₂-C₈)-alkylamino, (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl,

(C₀-C₄)-alkylene-(C₃-C₁₂)-heterocyclyl, (C₀-C₄)-alkylene-(C₃-C₁₂)-cycloalkyl, a bicyclic -(C₈-C₁₄) ring system, where aryl, heteroaryl, heterocyclyl, cycloalkyl or the bicyclic -(C₈-C₁₄) ring system may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₈)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

R¹ is hydrogen, (C₁-C₁₀)-alkyl, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl, -(C₃-C₁₂)-cycloalkyl; where alkyl may be substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl or -(C₃-C₁₂)-cycloalkyl, where aryl, heteroaryl, heterocyclyl or cycloalkyl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkyl-mercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

R² is hydrogen, (C₁-C₁₆)-alkyl or (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl;

R³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkyl-mercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, cyano, (C₁-C₆)-alkylcarbonyl, halogen, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl, or aminosulfonyl;

A is O, S, N(R²), C(R³) or C(R³)=C(R³);

B is C(R³) or N;

D is C(R³) or N; where at least one of the members A, B or D must be nitrogen;

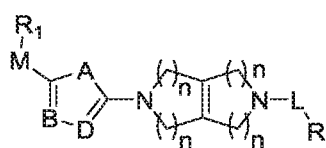
n is in each case independently 1 or 2;

L is a bond, -C(=O)-, -C(=S)-, -C(=O)-N(R²)-, -C(=O)-O-, -S(O)₀₋₂-, -S(O)₀₋₂-N(R²)-, a mono- or bicyclic ring system in which one or more ring members may be N(R³), O, S or -C(=O)-;

M is -O- or -O-CH₂-;

and physiologically compatible salts thereof.

In some embodiments, the compound of Formula XLVIII has the structure:



in which

R is hydrogen, (C₁-C₁₆)-alkyl, (C₁-C₅)-alkyloxy, (C₁-C₅)-alkylthio, (C₁-C₅)-alkylamino, di-(C₂-C₈)-alkylamino, (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl, (C₀-C₄)-alkylene-(C₃-C₁₂)-heterocyclyl, (C₀-C₄)-alkylene-(C₃-C₁₂)-cycloalkyl, a bicyclic -(C₈-C₁₄) ring system, where aryl, heteroaryl, heterocyclyl, cycloalkyl or the bicyclic -(C₈-C₁₄) ring system may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₈)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

R¹ is hydrogen, (C₁-C₁₀)-alkyl, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl, or -(C₃-C₁₂)-cycloalkyl;

where alkyl may be substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl,

(C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl or -(C₃-C₁₂)-cycloalkyl, where aryl, heteroaryl, heterocyclyl or cycloalkyl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

5 R² is hydrogen, (C₁-C₁₈)-alkyl, or (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl;

R³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, cyano, (C₁-C₆)-alkylcarbonyl, halogen, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl, or aminosulfonyl;

A is O, S, N(R²), C(R³), or C(R³)=C(R³);

10 B is C(R³) or N;

D is C(R³) or N;

where at least one of the members A, B or D must be nitrogen;

n is in each case independently 1 or 2;

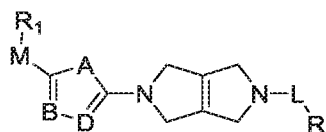
L is a bond, -C(=O)-, -C(=S)-, -C(=O)-N(R²)-, -S(O)₀₋₂-, -S(O)₀₋₂-N(R²)-, a mono- or bicyclic ring

15 system in which one or more ring members may be N(R³), O, S or -C(=O)-;

M is -O- or -O-CH₂-;

and physiologically compatible salts thereof.

In some embodiments, the compound of Formula XLVIII has the structure:



20 wherein

R is hydrogen, (C₁-C₁₈)-alkyl, (C₁-C₅)-alkyloxy, (C₁-C₅)-alkylthio, (C₁-C₅)-alkylamino, di-(C₂-C₈)-alkylamino, (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl, (C₀-C₄)-alkylene-(C₃-C₁₂)-heterocyclyl, (C₀-C₄)-alkylene-(C₃-C₁₂)-cycloalkyl, a bicyclic -(C₈-C₁₄) ring system, where aryl, heteroaryl, heterocyclyl, cycloalkyl or the bicyclic -(C₈-C₁₄) ring system may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₈)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

30 R¹ is (C₁-C₁₀)-alkyl, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl, -(C₃-C₁₂)-cycloalkyl, where alkyl may be substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl or -(C₃-C₁₂)-cycloalkyl, where aryl, heteroaryl, heterocyclyl or cycloalkyl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

35 R² is hydrogen, (C₁-C₁₈)-alkyl, or (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl;

R³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, cyano, (C₁-C₆)-alkylcarbonyl, halogen, trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl, or aminosulfonyl;

A is O, S, N(R²), C(R³), or C(R³)=C(R³);

B is C(R³), or N;

D is C(R³), or N;

where at least one of the members A, B or D must be nitrogen;

L is a bond, -C(=O)-, -C(=S)-, -C(=O)-N(R²)-, -C(=O)-O-, -S(O)₀₋₂-, -S(O)₀₋₂-N(R²)-, a mono- or
5 bicyclic ring system in which one or more ring members may be N(R³), O, S or -C(=O)-;

M is -O-, or -O-CH₂-;

and physiologically compatible salts thereof.

In some embodiments of the compound of Formula XLVIII, R is hydrogen, (C₁-C₁₆)-alkyl,
(C₁-C₅)-alkyloxy, (C₁-C₅)-alkylthio, (C₁-C₅)-alkylamino, di-(C₂-C₈)-alkylamino, (C₀-C₄)-alkylene-(C₆-C₁₀)-
10 aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl, (C₀-C₄)-alkylene-(C₃-C₁₂)-heterocyclyl, (C₀-C₄)-alkylene-(C₃-
C₁₂)-cycloalkyl, a bicyclic -(C₈-C₁₄) ring system, where aryl, heteroaryl, heterocyclyl, cycloalkyl or the
bicyclic -(C₈-C₁₄) ring system may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy,
hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-
alkylaminocarbonyl, di-(C₂-C₈)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano,
15 trifluoromethyl, trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

R¹ is (C₁-C₁₀)-alkyl, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl, -(C₃-C₁₂)-cycloalkyl,
where alkyl may be substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-
alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl,
-(C₃-C₁₂)-heterocyclyl or -(C₃-C₁₂)-cycloalkyl, where aryl, heteroaryl, heterocyclyl or cycloalkyl may
20 optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-
alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

R² is hydrogen, (C₁-C₁₆)-alkyl, or (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl;

R³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-
alkylamino, di-(C₂-C₁₂)-alkylamino, cyano, (C₁-C₆)-alkylcarbonyl, halogen, trifluoromethyl,
25 trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl, or aminosulfonyl;

A is S, or C(R³)=C(R³);

B is C(R³), or N;

D is N;

L is a bond, -C(=O)-, -C(=S)-, -C(=O)-N(R²)-, -C(=O)-O-, -S(O)₀₋₂-, -S(O)₀₋₂-N(R²)-, a mono- or
30 bicyclic ring system in which one or more ring members may be N(R³), O, S or -C(=O)-;

M is -O-, or -O-CH₂-;

and physiologically compatible salts thereof.

In some embodiments of the compound of Formula XLVIII, R is (C₁-C₁₆)-alkyl, (C₁-C₅)-alkyloxy,
(C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, a bicyclic -(C₈-C₁₄) ring system, where aryl or the bicyclic -(C₈-C₁₄) ring
35 system may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-
alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-alkylaminocarbonyl, di-
(C₂-C₈)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano, trifluoromethyl,
trifluoromethyloxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

R¹ is (C₁-C₁₀)-alkyl, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl, -(C₃-C₁₂)-heterocyclyl, -(C₃-C₁₂)-cycloalkyl,
40 where alkyl may be substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-
alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, -(C₆-C₁₀)-aryl, -(C₅-C₁₂)-heteroaryl,

-(C₃-C₁₂)-heterocyclyl or -(C₃-C₁₂)-cycloalkyl, where aryl, heteroaryl, heterocyclyl or cycloalkyl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

R² is hydrogen, (C₁-C₆)-alkyl, or (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl;

R³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, cyano, (C₁-C₆)-alkylcarbonyl, halogen, trifluoromethyl, trifluoromethoxy, (C₁-C₆)-alkylsulfonyl, or aminosulfonyl;

A is S, or C(R³)=C(R³);

B is C(R³), or N;

D is N;

L is a bond, or -C(=O)-;

M is -O-;

and physiologically compatible salts thereof.

In some embodiments of the compound of Formula XLVIII, R is (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, where aryl may be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, di-(C₂-C₁₂)-alkylamino, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, cyano, trifluoromethyl, trifluoromethoxy, (C₁-C₆)-alkylsulfonyl or aminosulfonyl;

R¹ is (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl, where aryl or heteroaryl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

R³ is hydrogen;

A is C(R³)=C(R³);

B is C(R³), N;

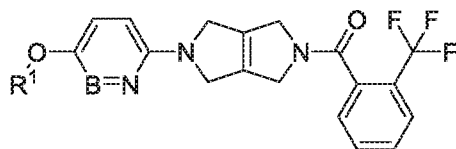
D is N;

L is -C(=O)-;

M is -O-;

and physiologically compatible salts thereof.

In some embodiments, the compound of Formula XLVIII has the structure:



in which

R¹ is (C₀-C₄)-alkylene-(C₆-C₁₀)-aryl, (C₀-C₄)-alkylene-(C₅-C₁₂)-heteroaryl, where aryl or heteroaryl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

B is CH, or N;

or physiologically compatible salts thereof.

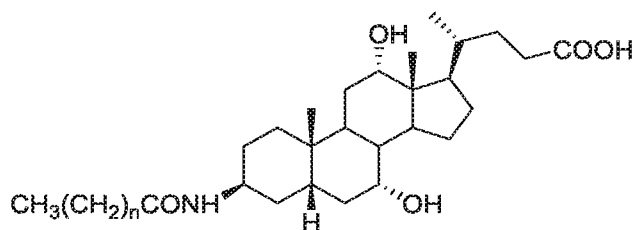
In some embodiments of the compound of Formula XLVIII, R¹ is (C₁-C₄)-alkylenepheryl,

(C₁-C₄)-alkylene-(C₅-C₆)-heteroaryl, where heteroaryl is a monocyclic aromatic ring with one or two ring heteroatoms selected from N, O or S and where phenyl or heteroaryl may optionally be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₁-C₃)-alkyloxy, hydroxyl, (C₁-C₆)-alkylmercapto, amino, (C₁-C₆)-alkylamino, or di-(C₂-C₁₂)-alkylamino;

- 5 B is CH, or N;
or physiologically compatible salts thereof.

Compounds of Formula (XLVIII) may be synthesized by methods known in the art, e.g., those described in U.S. Patent No. 8,673,917 B2. In some embodiments, the SCD inhibitor is a compound disclosed in U.S. Patent No. 8,673,917 B2, the compounds of which are herein incorporated by reference.

- 10 In some embodiments of any of the foregoing methods, the SCD inhibitor is a fatty acid-bile acid conjugate, e.g., a bile acid such as cholic acid conjugated with a fatty acid through an amide bond at position 3, or a pharmaceutically acceptable salt thereof. For example, in some embodiments, the SCD inhibitor has the structure of Formula XLIX:



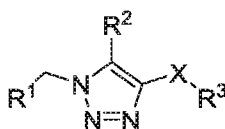
Formula XLIX

- 15 wherein n is an integer from 1 to 20,
or a pharmaceutically acceptable salt thereof.

In some embodiments, the SCD inhibitor is 3β-arachidylamido-7α,12α-dihydroxy-5β-cholan-24-oic acid, also known as Aramchol, or a pharmaceutically acceptable salt thereof.

- 20 In some embodiments of any of the foregoing methods, the SCD inhibitor is a 10,12 linoleic acid isomer or a pharmaceutically acceptable salt thereof. In some embodiments of any of the foregoing methods, the SCD inhibitor is an oxadiazole pyridazine or a pharmaceutically acceptable salt thereof. In some embodiments of any of the foregoing methods, the SCD inhibitor is a 1-(4-phenoxy piperidin-1-yl)-2-arylaminoethanone compound or a pharmaceutically acceptable salt thereof.
- 25 In some embodiments of any of the foregoing methods, the SCD inhibitor is a cyclopropenoid fatty acid or a pharmaceutically acceptable salt thereof. In some embodiments of any of the foregoing methods, the SCD inhibitor is a thia-fatty acid or a pharmaceutically acceptable salt thereof. In some embodiments of any of the foregoing methods, the SCD inhibitor is pioglitazone, rosiglitazone, ciglitazone, englitazone, troglitazone, leptin, or a pharmaceutically acceptable salts thereof.

- 30 In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula L:



Formula L

wherein X represents -CONH-, -NHCO- or -CH₂NH-;

R¹ represents -C₆₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from:

(a) -C₁₋₆alkyl (such as -CH₃, or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₅cycloalkyl or halogen (such as chloro, bromo or fluoro);

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro, bromo or fluoro);

R² represents hydrogen or -C₁₋₆alkyl (such as -CH₃);

R³ represents -C₆₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from:

(a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅alkenyl, -C₁₋₅alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH (such as -CH₂OH, -C(CH₃)₂OH or -CH(CH₃)OH), -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₅alkylOH, -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₅cycloalkyl or halogen (such as chloro, bromo or fluoro);

(b) -C₅heteroaryl (such as oxazole);

R⁴ represents -C₆₋₁₀aryl (such as phenyl);

R⁵ represents -H or -C₁₋₆alkyl (such as -CH₃);

R⁶ represents -H or -C₁₋₃alkyl (such as -CH₃) or -C₁₋₃alkylOH;

R⁷ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁸ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁹ represents -H or -C₁₋₃alkyl (such as -CH₃);

m represents 1-3;

n represents 0-3;

p represents 0-3; and

q represents 1-3;

or a pharmaceutically acceptable salt thereof.

In some embodiments, X represents -CONH-. In some embodiments, X represents -NHCO-. In some embodiments, X represents -CH₂NH-. In some embodiments, X represents -CONH- or -CH₂NH-.

In some embodiments, R¹ represents phenyl substituted by one, two or three groups independently selected from:

(a) -C₁₋₅alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₅cycloalkyl or halogen (such as chloro, bromo or fluoro),

(b) phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

In some embodiments, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₅cycloalkyl or halogen (such as chloro, bromo or fluoro),

(b) phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

In some embodiments, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₅alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₅cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -CH₃, -CH(CH₃)₂ or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -CH₃, -CH(CH₃)₂ or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl substituted by two groups independently selected from halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl substituted by a group independently selected from halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl substituted by phenyl optionally substituted by halogen (such as chloro, bromo or fluoro). In some embodiments, R¹ represents phenyl substituted by phenyl. In some embodiments, R¹ represents phenyl substituted by two chloro groups. In some embodiments, R¹ is phenyl substituted in the meta position, that is in the 3 position, and the para position, that is in the 4 position, by halogen e.g chloro. In some embodiments, R¹ is phenyl substituted in the meta position, that is in the 3 position and 5 position, by halogen e.g chloro. In some embodiments, R¹ is phenyl.

In some embodiments, R^2 represents hydrogen. In some embodiments, R^2 represents $-C_{1-6}$ alkyl. In some embodiments, R^2 represents $-C_{1-3}$ alkyl. In some embodiments, R^2 represents $-CH_3$ (methyl). In some embodiments, R^2 represents hydrogen or $-C_{1-3}$ alkyl.

In some embodiments, R^3 represents phenyl optionally substituted by one, two or three groups independently selected from: (a) $-C_{1-6}$ alkyl (such as $-CH_3$), $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-5}$ haloalkyl (such as $-CF_3$), $-OC_{1-5}$ haloalkyl (such as $-OCF_3$), $-C_{3-5}$ cycloalkyl, $-OC_{3-5}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by one or two groups independently selected from: (a) $-C_{1-5}$ alkyl (such as $-CH_3$), $-C_{1-5}$ alkenyl, $-C_{1-5}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-5}$ haloalkyl (such as $-CF_3$), $-OC_{1-5}$ haloalkyl (such as $-OCF_3$), $-C_{3-5}$ cycloalkyl, $-OC_{3-5}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one, two or three groups independently selected from: (a) $-C_{1-6}$ alkyl (such as $-CH_3$), $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-5}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-5}$ haloalkyl (such as $-CF_3$), $-OC_{1-5}$ haloalkyl (such as $-OCF_3$), $-C_{3-5}$ cycloalkyl, $-OC_{3-5}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one or two groups independently selected from: (a) $-C_{1-5}$ alkyl (such as $-CH_3$), $-C_{1-5}$ alkenyl, $-C_{1-5}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-5}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-5}$ haloalkyl (such as $-CF_3$), $-OC_{1-5}$ haloalkyl (such as $-OCF_3$), $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one, two or three groups independently selected from: (a) $-C_{1-3}$ alkyl (such as $-CH_3$), $-C_{1-3}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-3}$ haloalkyl (such as $-CF_3$), $-OC_{1-3}$ haloalkyl (such as $-OCF_3$), $-C_{3-5}$ cycloalkyl, $-OC_{3-5}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one or two groups independently selected from: (a) $-C_{1-3}$ alkyl (such as $-CH_3$), $-C_{1-3}$ alkenyl, $-C_{1-5}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-5}$ alkylOH, $-C_{1-3}$ haloalkyl (such as $-CF_3$), $-OC_{1-3}$ haloalkyl (such as $-OCF_3$), $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) $-C_5$ heteroaryl (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group

independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one, two or three groups independently selected from: (a) $-C_{1-3}alkyl$ (such as $-CH_3$), $-C_{1-3}alkenyl$, $-C_{1-5}alkoxy$ (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}alkylOH$ (such as $-CH_2OH$, $-CH(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}alkylOH$ or halogen (such as chloro, bromo or fluoro), (b) $-C_5heteroaryl$ (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one or two groups independently selected from: (a) $-C_{1-3}alkyl$ (such as $-CH_3$), $-C_{1-3}alkenyl$, $-C_{1-5}alkoxy$ (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}alkylOH$ (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}alkylOH$ or halogen (such as chloro, bromo or fluoro), (b) $-C_5heteroaryl$ (such as oxazole). In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or, (ii) one, two or three groups independently selected from: (a) $-C_{1-3}alkyl$ (such as $-CH_3$), $-C_{1-3}alkenyl$, $-C_{1-5}alkoxy$ (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}alkylOH$ (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}alkylOH$ or halogen (such as chloro, bromo or fluoro), (b) oxazole. In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NHC_2H_5$ or $-C(=O)NHC_2H_4OH$ and/or, (ii) one, two or three groups independently selected from: (a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, $-CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $-NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, $-OC_2H_4OH$ or halogen (such as chloro, bromo or fluoro), (b) oxazole. In some embodiments, R^3 represents phenyl optionally substituted by: (i) one group independently selected from $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NHC_2H_5$ or $-C(=O)NHC_2H_4OH$ and/or, (ii) one or two groups independently selected from: (a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, $-CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $-NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, $-OC_2H_4OH$ or halogen (such as chloro, bromo or fluoro), (b) oxazole. In some embodiments, R^3 represents phenyl optionally substituted by one or two $-CH_2OH$ groups. In some embodiments, R^3 represents phenyl substituted by one or two $-CH_2OH$ groups. In some embodiments, R^3 represents phenyl substituted in the meta position, that is in the 3 and 5 position, by $-CH_2OH$. In some embodiments, R^3 represents phenyl substituted in the meta position, that is in the 3 position and the para position, that is in the 4 position, by $-CH_2OH$. In some embodiments, R^3 represents phenyl substituted by $-CH_2OH$.

In some embodiments, R^4 represents phenyl.

In some embodiments, R^5 represents hydrogen. In some embodiments, R^5 represents $-C_{1-6}alkyl$.

In some embodiments, R^5 represents $-C_{1-3}alkyl$. In some embodiments, R^5 represents ethyl. In some embodiments, R^5 represents methyl.

In some embodiments, R^6 represents hydrogen. In some embodiments, R^6 represents $-C_{1-3}alkyl$. In some embodiments, R^6 represents ethyl. In some embodiments, R^6 represents methyl. In some embodiments, R^6 represents $-C_{1-3}alkylOH$. In some embodiments, R^6 represents $-C_2H_4OH$.

In some embodiments, R^7 represents hydrogen. In some embodiments, R^7 represents $-C_{1-3}alkyl$. In some embodiments, R^7 represents methyl.

In some embodiments, R⁸ represents hydrogen. In some embodiments, R⁸ represents -C₁₋₃alkyl. In some embodiments, R⁸ represents methyl.

In some embodiments, R⁹ represents hydrogen. In some embodiments, R⁹ represents -C₁₋₃alkyl. In some embodiments, R⁹ represents methyl.

5 In some embodiments, m represents 1 or 2. In some embodiments, m represents 2. In some embodiments, m represents 1.

In some embodiments, n represents 0, 1 or 2. In some embodiments, n represents 3. In some embodiments, n represents 2. In some embodiments, n represents 1. In some embodiments, n represents 0.

10 In some embodiments, p represents 0, 1 or 2. In some embodiments, p represents 2. In some embodiments, p represents 1. In some embodiments, p represents 0.

In some embodiments, q represents 1 or 2. In some embodiments, q represents 2. In some embodiments, q represents 1.

In some embodiments, the SCD inhibitors is N-[3,4-bis(methoxy)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-bis(methoxy)phenyl]-1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 5-Methyl-1-(phenylmethyl)-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, 1-[(2'-Chloro-4-biphenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide, 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide, 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[[4-(1-methylethyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, N-[3,4-Bis(methoxy)phenyl]-5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide, 1-(2-Biphenylmethyl)-N-[3,4-bis(methoxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-Bis(methoxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1,3-oxazol-2-yl)phenyl]-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, Methyl-4-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-3-(methoxy)benzoate, 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{3-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{4-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide, Ethyl-3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]benzoate, N-[3-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[4-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, Methyl-3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-4-(methoxy)benzoate, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, Ethyl-4-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-

yl}carbonyl)amino]phenyl}acetate, Methyl-4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-2-(methyloxy)benzoate, Methyl-5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-2-hydroxybenzoate, Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]phenyl}acetate, 1-[(3,4-Dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide, Methyl-5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-2-fluorobenzoate, N-[5-(Aminocarbonyl)-2-(methyloxy)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, Methyl 4-chloro-3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]benzoate, Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-4-(methyloxy)phenyl}acetate,

10 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-4-fluorobenzoate, N-[3-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-[4-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

15 Methyl 3-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-4-(methyloxy)benzoate, 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3-[(Acetylamino)methyl]phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[4-chloro-3-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, Dimethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-1,2-benzenedicarboxylate, Methyl 5-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-2-fluorobenzoate, Ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]benzoate, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,5-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[5-(2-hydroxyethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[2-fluoro-5-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[2-chloro-5-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,5-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,5-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]benzoic acid, 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-4-(methyloxy)benzoic acid, 5-[(5-Methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-

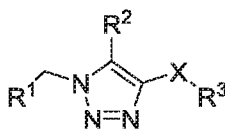
yl]carbonyl]amino)-1,3-benzenedicarboxylic acid, 4-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid, 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(ethylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(2-hydroxyethyl)amino]carbonyl}phenyl-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[5-[(methylamino)carbonyl]-2-(methoxy)phenyl]-1H-1,2,3-triazole-4-carboxamide, {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino}phenyl)methylacetate, {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino}phenyl)methylacetate, {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino}phenyl)methylbenzoate, {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino}phenyl)methylbenzoate, 1-[(3,4-Dichlorophenyl)methyl]-N-{4-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1-methylethenyl)-2-(methoxy)phenyl]-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxy-1-methylethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-[4-[(2-(dimethylamino)ethyl)oxy]-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, or {5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)methyl]amino}benzene-1,3-diyl}dimethanol, or a pharmaceutically acceptable salt thereof.

In some embodiments, the SCD inhibitor is N-[3,4-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-chlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(4-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-chlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(4-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-dichlorophenyl)methyl]-N-{3-(hydroxymethyl)-5-[(methylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, or N-{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}-4-(hydroxymethyl)benzamide, or a pharmaceutically acceptable salt thereof.

In some embodiments, the SCD inhibitor is N-{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}-4-(hydroxymethyl)benzamide, or a pharmaceutically acceptable salt thereof.

Compounds of Formula L may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/060053.

In some embodiments of any of the foregoing methods, the SCD inhibitor is a compound of Formula LI:



Formula LI

wherein X represents -CONH-, -NHCO- or -CH₂NH-;

R¹ represents: -C₆₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃), -C₁₋₅alkoxy (such as -OCH₃), -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -OC₃₋₅cycloalkyl or halogen (such as chloro, bromo or fluoro);

R² represents hydrogen, -C₁₋₆alkyl (such as -CH₃) or -C₁₋₃alkylOC₁₋₃alkyl (such as -CH₂OCH₃);

R³ represents: -C₅₋₉heteroaryl optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃), -C₁₋₆alkoxy (such as -OCH₃), -CO₂R⁴, -C(=O)NR⁵R⁶, -C(=O)NHC₁₋₃alkylNR⁷R⁸, -C(=O)NHC₁₋₃alkylOC₁₋₃alkyl, -C(=O)NHC₁₋₃alkylOH, -C(=O)R⁹, -C₁₋₆alkylOH (such as -CH₂OH or -C₂H₄OH), -C=O, -CHO, -C₁₋₃alkylCO₂C₁₋₃alkyl, -C₁₋₃alkylOC₁₋₃alkyl, -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -OC₃₋₆cycloalkyl, -C₃₋₆cycloalkyl, or halogen (such as chloro, bromo or fluoro);

R⁴ represents -H or -C₁₋₃alkyl (such as -CH₃ or -C₂H₅);

R⁵ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁶ represents -H or -C₁₋₃alkyl (such as -CH₃);

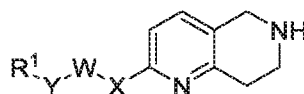
R⁷ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁸ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁹ represents -C₆heterocycle (such as morpholine or piperazine) which is optionally substituted by a group independently selected from: -C₁₋₆alkyl (such as -CH₃); or a pharmaceutically acceptable salt thereof.

Compounds of Formula LI may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/060054. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/060054, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LII:



Formula LII

wherein X represents -CONH- or -NHCO-;

R¹ represents: (i) a substituent selected from: H, -C₁₋₅alkyl, -C₃₋₅cycloalkyl or -C₃₋₅cycloalkenyl; (ii) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from (a) -C₁₋₃alkyl (such as -CH₃), -C₁₋₅alkoxy (such as -OCH₃ or -OC₄H₉), -C₁₋₅haloalkyl (such as CF₃), -C₃₋₆cycloalkyl, -OC₁₋₅haloalkyl (such as -OCF₃), -CN, or halogen (such as chloro, bromo or fluoro); (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₅alkyl (such as -CH₃), -C₁₋₅alkoxy (such as -OCH₃), -C₁₋₅haloalkyl (such as -CF₃) or halogen (such as chloro, bromo or fluoro);

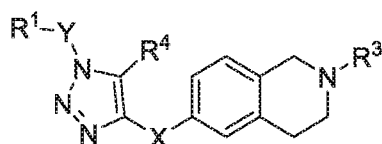
Y represents -CH₂- or -OCH₂-; and

W represents a -C₅₋₁₀heteroaryl optionally substituted by one, two or three -C₁₋₆alkyl (such as -CH₃) groups;

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LII may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/056556. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/056556, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LIII:



Formula LIII

wherein X represents -CONH- or -NHCO-;

R¹ represents (i) a substituent selected from: -H or -C₁₋₆alkyl, (ii) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₂alkyl (such as methyl), -C₁₋₆haloalkyl (such as -CF₃) or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₆₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl, -C₁₋₅alkoxy, or -C₁₋₆haloalkyl (such as -CF₃), (iii) benzothiophene or thiophene wherein the benzothiophene or thiophene is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl, -C₁₋₆haloalkyl (such as -CF₃), or halogen (such as chloro, bromo or fluoro),

Y represents -CH₂- or -OCH₂-,

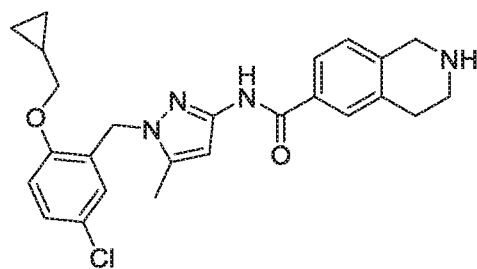
R² represents H,

R³ represents -H or -C₁₋₂alkyl (such as methyl),

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LIII may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/016216. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/016216, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LIV:

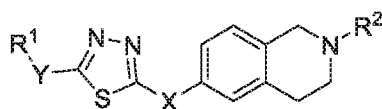


Formula LIV

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LIV may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/010560. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/010560, the compounds of which are herein incorporated by reference.

5 In some embodiments, the SCD inhibitor is a compound of Formula LV:



Formula LV

wherein X represents -CONH-, -NHCO- or -N(CH₃)CO-,

R¹ represents (i) a substituent selected from: H, -C₁₋₆alkyl or -C₃₋₆cycloalkyl, (ii) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₃₋₆cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₁₋₆alkoxy (such as -OCH₃), -OR³, -CN or halogen (such as chloro, bromo or fluoro), (iii) -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl is optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN or halogen (such as chloro, bromo or fluoro), (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN or halogen (such as chloro, bromo or fluoro),

Y represents -(CH₂)_m-, -O(CH₂)_m- or -NR⁷(CH₂)_m-,

R² represents H, -C₁₋₅alkyl, -C(=O)C₁₋₆alkyl, -C(=O)C₃₋₅cycloalkyl, -C(=O)C₆₋₁₀aryl, -C(=O)C₁₋₅alkylOH, -COC₁₋₃alkylNR⁴R⁵ or -C₅heteroarylR⁶,

R³ represents -C₁₋₅haloalkyl (such as -CF₃) or -C₃₋₆cycloalkyl,

R⁴ represents H or -C₁₋₃alkyl (such as -CH₃),

R⁵ represents H or -C₁₋₃alkyl (such as -CH₃),

R⁶ represents -C₁₋₃alkylOH,

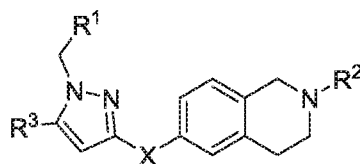
R⁷ represents H or -C₁₋₃alkyl (such as -CH₃), and

m represents integers from 1 to 4,

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LV may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/104524. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/104524, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LVI:



Formula LVI

wherein X represents -CONH- or -NHCO-;

R¹ represents -C₅₋₁₀aryl (such as phenyl) substituted by -C₁₋₅alkoxy or -OC₁₋₅haloalkyl (such as -OCF₃), and is further optionally substituted by one or two groups independently selected from: (a) -C₁₋₅alkyl, -C₁₋₅alkoxy, -C₁₋₅haloalkyl (such as -CF₃), -OC₁₋₅haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl, -OR⁵, -C₁₋₆haloalkyl (such as CF₃) or halogen (such as chloro, bromo or fluoro);

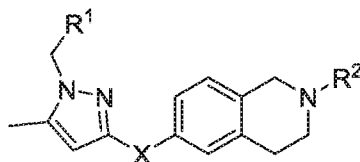
R² represents H or -C₂₋₆alkyl; and

R³ represents -C₂₋₅alkyl or -C₃₋₅cycloalkyl;

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LVI may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/074834. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/074834, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LVII:



Formula LVII

wherein X represents -CONH- or -NHCO-;

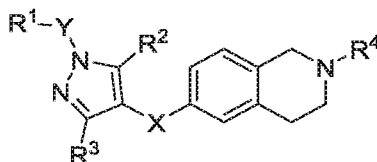
R¹ represents phenyl substituted by -OCH₃ or -OCF₃ and is further optionally substituted by one or two or three groups independently selected from: -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro); and

R² represents H or -C₂₋₆alkyl;

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LVII may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/074833. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/074833, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LVIII:



Formula LVIII

wherein X represents -CONH-, -NHCO- or -NHCONH-,

R¹ represents (i) a substituent selected from: H, -C₁₋₅alkyl or -C₃₋₅cycloalkyl, (ii) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₆alkoxy (such as -OCH₃), -OR⁵, -CN or halogen (such as chloro, bromo or fluoro), (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₆₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃), -OR⁵, -C₁₋₆alkoxy (such as -OCH₃), -C₁₋₆haloalkyl (such as -CF₃), -CN or halogen (such as chloro, bromo or fluoro), (iii) -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl is optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR⁵, -CN or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃), -OR⁵, -C₁₋₆alkoxy (such as -OCH₃), -C₁₋₆haloalkyl (such as -CF₃), -CN or halogen (such as chloro, bromo or fluoro),

Y represents -(CH₂)_m- or -O(CH₂)_m-,

one of R² or R³ represents hydrogen and the other represents H, -C₁₋₆alkyl (such as -CH₃) or -C₃₋₅cycloalkyl,

R⁴ represents H, -C₁₋₆alkyl, -C(=O)C₁₋₆alkyl, -C(=O)C₃₋₆cycloalkyl, or -CO₂C₁₋₆alkyl,

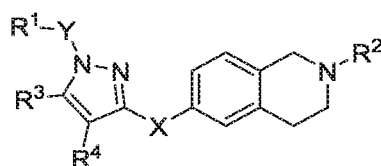
R⁵ represents -C₁₋₆haloalkyl (such as -CF₃) or -C₃₋₆cycloalkyl, and

m represents integers from 1 to 3,

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LVIII may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/074824. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/074824, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LIX:



Formula LIX

wherein X represents -CONH- or -NHCO-;

R¹ represents (i) a substituent selected from: -C₁₋₆alkyl or -C₃₋₆cycloalkyl, (ii) -C₅₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl, -OR⁵, -C₁₋₆haloalkyl (such as -CF₃) or halogen (such as chloro,

bromo or fluoro), (iii) -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl is optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl, -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy, -OC₁₋₆haloalkyl, -O(CH₂)_nC₃₋₆cycloalkyl, -OR⁵ or halogen (such as chloro, bromo or fluoro), (b) -C₅₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl, -OR⁵, -C₁₋₆haloalkyl (such as -CF₃) or halogen (such as chloro, bromo or fluoro),

R² represents H or -C₂₋₆alkyl;

R³ and R⁴ independently represent hydrogen, -C₁₋₆alkyl (such as methyl) or -C₃₋₆cycloalkyl with the proviso that R³ and R⁴ do not both represent hydrogen;

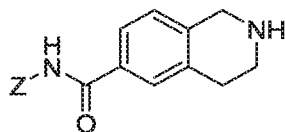
R⁵ represents -C₁₋₆haloalkyl (such as -CF₃) or -C₃₋₆cycloalkyl; and

n represents integers from 0 to 6;

or a pharmaceutically acceptable salt thereof.

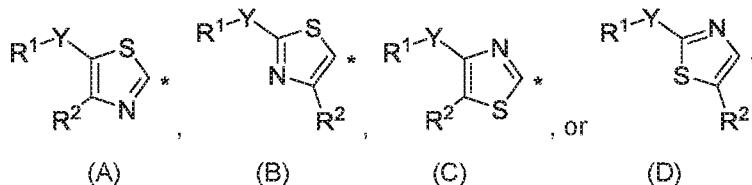
Compounds of Formula LIX may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2008/074832. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2008/074832, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LX:



Formula LX

wherein Z represents:



where * represents the point of attachment,

when Z represents (A) or (B) then R¹ represents (i) H or -C₁₋₆alkyl, (ii) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₃₋₆cycloalkyl, -C₁₋₆alkoxy (such as -OCH₃ or -OCH₂CH(CH₃)₂), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₆alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (iii) -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl is optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₆alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as

phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro),

5 Y represents -(CH₂)_m- or -CONHCH₂-,

R² represents H, -C₁₋₅alkyl (such as -CH₃, -C₂H₄ or -C₃H₇) or -C₃₋₅cycloalkyl,

R³ represents -C₁₋₆haloalkyl (such as -CF₃) or -C₃₋₆cycloalkyl, and

m represents 1 or 2,

when Z represents (C) or (D) than

10 R¹ represents: (i) -C₆₋₁₀aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl, wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from:
15 -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (ii) -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl is optionally substituted by one, two or three groups independently selected from: (a) -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₆alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro), (b) -C₆₋₁₀aryl
20 (such as phenyl), -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl wherein the -C₅₋₁₀aryl, -C₅₋₁₀heteroaryl or -C₅₋₁₀heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C₁₋₅alkyl (such as -CH₃), -C₁₋₅haloalkyl (such as -CF₃), -C₃₋₅cycloalkyl, -C₁₋₅alkoxy (such as -OCH₃), -OR³, -CN, -NO₂ or halogen (such as chloro, bromo or fluoro),

Y represents -(CH₂)_m-,

25 R² represents H, -C₁₋₅alkyl (such as -CH₃ or -C₂H₄) or -C₃₋₅cycloalkyl,

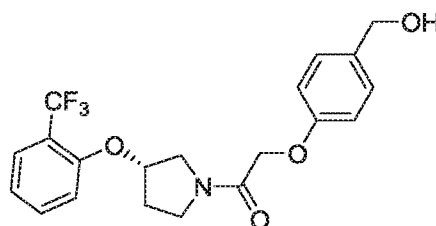
R³ represents, -C₁₋₆haloalkyl (such as -CF₃) or -C₃₋₆cycloalkyl, and

m represents 0, 1, or 2,

or a pharmaceutically acceptable salt thereof.

Compounds of Formula LX may be synthesized by methods known in the art, e.g., those
30 described in International Patent Publication No. WO2009/150196. In some embodiments, the SCD inhibitor is a compound disclosed in International Patent Publication No. WO2009/150196, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound of Formula LXI:



35 Formula LXI

Compounds of Formula LXI may be synthesized by methods known in the art, e.g., those described in International Patent Publication No. WO2009/019566. In some embodiments, the SCD

inhibitor is a compound disclosed in International Patent Publication No. WO2009/019566, the compounds of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a compound disclosed in any one of International Patent Publication Nos. WO2015/137385, WO2015/132610, WO2014/116386, WO2013/160811, WO2012/046681, WO2011/131593, WO2011/030312, WO2011/015629, WO2010/045374, WO2010/045371, WO2010/035052, WO2010/006962, WO2010/007482, WO2009/124259, WO2013/134546, WO2013/085954, WO2013/085957, WO2011/011508, WO2011/011506, WO2010/056230, WO2009/070533, WO2009/037542, WO2008/139845, WO2008/120744, WO2008/120759, WO2008/123469, WO2008/116898, WO2008/096746, WO2008/062276, WO2008/056687, WO2008/044767, WO2008/043087, WO2008/029266, WO2008/003753, WO2006/057902, WO2006/015621, WO2005/011657, and WO1999/063979, U.S. Patent Publication Nos. US2012/252850, US2010/160323, US2009/253738, US2009/170822, US2009/253693, US2009/149466, US2008/249100, US2008/255130, US2008/255161, US2007/087363, and US2005/119242, Japanese Patent Publication Nos. JP2010/043052, JP2009/019013, and JP2005/213233, and Korean Patent Publication Nos. KR2015/014719 and KR2015/015305, the compounds of each of which are herein incorporated by reference.

In some embodiments, the SCD inhibitor is a nucleic acid molecule capable of mediating RNA interference against SCD genes. For example, in some embodiments, the SCD inhibitor is a small nucleic acid molecule such as a short interfering nucleic acid (siNA), a short interfering RNA (siRNA), a double-stranded RNA (dsRNA), a micro-RNA (miRNA), or short hairpin RNA (shRNA) capable of mediating RNA interference against SCD genes. Nucleic acid molecules capable of mediating RNA interference against SCD genes may be synthesized by methods known in the art, e.g., those described in International Patent Publication Nos. WO2003/070885 and WO2005/014607 and U.S. Patent Publication No. US2005/0256068. In some embodiments, the SCD inhibitor is a nucleic acid molecule disclosed in International Patent Publication Nos. WO2003/070885 or WO2005/014607, or U.S. Patent Publication No. US2005/0256068, the nucleic acid molecules of each of which are herein incorporated by reference.

Chemical Terms

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

The term "acyl," as used herein, represents a hydrogen or an alkyl group, as defined herein, that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms). An alkylene is a divalent alkyl group.

The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2 , $N(R^{N2})_2$, SO_2OR^{N2} , SO_2R^{N2} , SOR^{N2} , an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$).

The term "aryl," as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{6-10} aryl, C_{1-10} alkyl C_{6-10} aryl, or C_{1-20} alkyl C_{6-10} aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "azido," as used herein, represents a $-N_3$ group.

The term "cyano," as used herein, represents a $-CN$ group.

The terms "carbocyclyl," as used herein, refer to a non-aromatic C_{3-12} monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups and unsaturated carbocyclyl radicals.

The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

The term "halogen," as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers alkyl-O- (e.g., methoxy and ethoxy). A heteroalkylene is a divalent heteroalkyl group.

The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an "alkenoxy" which, as used herein, refers alkenyl-O-. A heteroalkenylene is a divalent heteroalkenyl group.

The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as

described herein for alkynyl groups. Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers alkynyl-O-. A heteroalkynylene is a divalent heteroalkynyl group.

The term "heteroaryl," as used herein, refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxazolyl, and thiazolyl.

The term "heteroarylalkyl," as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁₋₆alkyl C₂₋₉heteroaryl, C₁₋₁₀alkyl C₂₋₉heteroaryl, or C₁₋₂₀alkyl C₂₋₉heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "heterocyclyl," as used herein, denotes a mono- or polycyclic radical having 3 to 12 atoms having at least one ring containing one, two, three, or four ring heteroatoms selected from N, O or S, wherein no ring is aromatic. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranlyl, and 1,3-dioxanyl.

The term "heterocyclylalkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁₋₆ alkyl C₂₋₉ heterocyclyl, C₁₋₁₀ alkyl C₂₋₉ heterocyclyl, or C₁₋₂₀ alkyl C₂₋₉ heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "hydroxyl," as used herein, represents an -OH group.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl.

Preferred *N*-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, *t*-butylacetyl, alanyl, phenylsulfonyl, benzyl, *t*-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "nitro," as used herein, represents an -NO₂ group.

The term "thiol," as used herein, represents an -SH group.

5 The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, 10 ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH₂ or mono- or dialkyl amino), azido, cyano, nitro, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds of the invention can have one or more asymmetric carbon atoms and can exist in the 15 form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric 20 forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more 25 asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can 30 be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. "Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on 35 opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may 40 be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an

isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9%) by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Definitions

The term "alpha-synuclein" refers to proteins whose amino acid sequence comprises or consists of an amino acid sequence of a naturally occurring wild-type alpha-synuclein protein as well as proteins whose amino acid sequence comprises or consists of an amino acid sequence of a naturally occurring mutant alpha-synuclein protein. Alpha-synuclein is also referred to as synuclein alpha (SNCA). Human alpha-synuclein has NCBI Gene ID NO 6622. Alpha-synuclein is considered an intrinsically disordered

protein. Naturally occurring mutant alpha-synuclein proteins include A53T, A30P, E46K, H50Q, and G51D.

As used herein, "alpha-synuclein-induced toxicity" and "alpha-synuclein-mediated toxicity" are used interchangeably to refer to a reduction, impairment, or other abnormality in one or more cellular functions or structures, a reduction in growth or viability, or a combination thereof, occurring as a result of or associated with expression of an alpha-synuclein protein. In the context of a yeast cell, alpha-synuclein-mediated toxicity may be manifested as a reduction in growth or viability, e.g., reduced viability or non-viability, or a reduction, impairment, or other abnormality in one or more cellular functions or structures, e.g., reduction, impairment, or other abnormality in endocytosis or vesicle trafficking. In the context of a neuron or glial cell, e.g., a mammalian neuron or glial cell, alpha-synuclein-mediated toxicity may be manifested as a reduction in growth or viability, e.g., reduced viability or non-viability, or a reduction, impairment, or other abnormality in one or more cellular functions or structures. Cellular functions include any of the biological processes and pathways performed in a cell or by a cell, either itself or together with one or more other cells, in vitro or in vivo (e.g., in the context of a tissue or organ in vivo). In some embodiments, a cellular function is endocytosis, vesicle trafficking, axonal transport, mitochondrial function (e.g., ATP production), neurite outgrowth, neurotransmission, neurogenesis, or maintaining homeostasis. Alpha-synuclein-mediated toxicity in vivo may be manifested to a variety of extents and in a variety of ways ranging from cellular dysfunction to death. In some embodiments alpha-synuclein-mediated toxicity may be evidenced in a subject by development of a synucleinopathy or by an increased propensity to develop a synucleinopathy. In some embodiments alpha-synuclein-mediated toxicity may be manifested as a decrease or defect in cognition, behavior, or memory, as compared with a normal control. In some embodiments, contacting mammalian cells or treating a mammalian subject with an agent as described herein alleviates one or more manifestations of alpha-synuclein-mediated toxicity.

The term "apolipoprotein E (ApoE)" refers to proteins whose amino acid sequence comprises or consists of an amino acid sequence of a naturally occurring wild type ApoE protein as well as proteins whose amino acid sequence comprises or consists of an amino acid sequence of a naturally occurring allelic variant ApoE protein. Human APOE has NCBI Gene ID NO 348. APOE has three common alleles in humans: APOE ϵ 2 (frequency ~8%), APOE ϵ 3 (frequency ~80%), and APOE ϵ 4 (frequency ~14%). The proteins encoded by the three common APOE alleles differ at two amino acids, located at positions 112 and 158 in the mature protein. ApoE2 has cysteine at residues 112 and 158; ApoE3 has cysteine at residue 112 and arginine at residue 158; and ApoE4 has arginine at residues 112 and 158. Human ApoE protein is naturally synthesized as a precursor polypeptide of 317 amino acids, including an 18 amino acid signal sequence, which is cleaved to produce the mature 299 amino acid polypeptide. The sequence of human ApoE3 precursor polypeptide is found under NCBI RefSeq Acc. No. NP_000032.1. Naturally occurring ApoE mutations include ApoE4(L28P), which confers on carriers an increased risk for late-onset AD that remains significant even after adjusting for the effect of ApoE4 itself (Kamboh et al. *Neurosci Lett.* 263(2-3):129-32, 1999). Other variants include E13K, R136C, G196S, Q248E, R251G, and G278W (Tindale et al., *Neurobiology of Aging* 35, 727e1- 727e3, 2014).

As used herein, "ApoE-induced toxicity" and "ApoE-mediated toxicity" are used interchangeably to refer to a reduction, impairment, or other abnormality in one or more cellular functions or structures, a

reduction in growth or viability, or a combination thereof, occurring as a result of or associated with expression of an ApoE protein. In the context of a yeast cell, ApoE-mediated toxicity may be manifested as a reduction in growth or viability, e.g., reduced viability or non-viability, or a reduction, impairment, or other abnormality in one or more cellular functions or structures, e.g., reduction, impairment, or other abnormality in endocytosis or vesicle trafficking. In the context of a neuron or glial cell, e.g., a mammalian neuron or glial cell, ApoE-mediated toxicity may be manifested as a reduction in growth or viability, e.g., reduced viability or non-viability, or a reduction, impairment, or other abnormality in one or more cellular functions or structures. Cellular functions include any of the biological processes and pathways performed in a cell or by a cell, either itself or together with one or more other cells, in vitro or in vivo (e.g., in the context of a tissue or organ in vivo). In some embodiments, a cellular function is endocytosis, vesicle trafficking, axonal transport, mitochondrial function (e.g., ATP production), neurite outgrowth, neurotransmission, neurogenesis, or maintaining homeostasis. ApoE-mediated toxicity in vivo may be manifested to a variety of extents and in a variety of ways ranging from cellular dysfunction to death. In some embodiments ApoE-mediated toxicity may be evidenced in a subject by development of an ApoE-mediated disease (or one or more symptoms or signs of an ApoE-mediated disease) or by an increased propensity to develop an ApoE-mediated disease in subjects who express a particular ApoE isoform. In some embodiments ApoE-mediated toxicity may be manifested at least in part as an increase in the formation, deposition, accumulation, or persistence of amyloid beta aggregates or an increase in amyloid beta-mediated toxicity as compared with a normal control. In some embodiments ApoE-mediated toxicity may be manifested as a decrease or defect in cognition, behavior, or memory, as compared with a normal control. In some embodiments, contacting mammalian cells or treating a mammalian subject with an agent as described herein alleviates one or more manifestations of ApoE-mediated toxicity.

By "determining the level of a protein" is meant the detection of a protein or mRNA by methods known in the art either directly or indirectly. "Directly determining" means performing a process (e.g., performing an assay or test on a sample or "analyzing a sample" as that term is defined herein) to obtain the physical entity or value. "Indirectly determining" refers to receiving the physical entity or value from another party or source (e.g., a third party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

In the practice of the methods of the present invention, an "effective amount" of any one of the compounds of the invention or a combination of any of the compounds of the invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination.

By "level" is meant a level of a protein or mRNA, as compared to a reference. The reference can be any useful reference, as defined herein. By a "decreased level" or an "increased level" of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, µg/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

A "neurodegenerative disorder" refers to a disorder characterized by progressive loss of the number (e.g., by cell death), structure, and/or function of neurons. In some instances, a neurodegenerative disease may be associated with protein misfolding, defects in protein degradation, genetic defects, programmed cell death, membrane damage, or other processes. Exemplary, non-limiting neurodegenerative disorders include AD, PD, ApoE-associated neurodegenerative disorders, Alpers' disease, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Kennedy's disease, Krabbe disease, Pelizaeus-Merzbacher disease, primary lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, Steele-Richardson-Olszewski disease, tabes dorsalis, vascular dementia, and Guillain-Barre Syndrome.

An "ApoE-associated neurodegenerative disorder" refers to a neurodegenerative disorder that is associated with and/or mediated at least in part by an ApoE protein (e.g., ApoE4). Exemplary ApoE-associated neurodegenerative disorders include, e.g., Alzheimer's disease (AD), dementia with Lewy bodies (DLB; also referred to as "Lewy body dementia"), mild cognitive impairment (MCI), frontotemporal dementia (FTD), cerebral amyloid angiopathy (CAA), CAA-associated intracerebral hemorrhage, vascular cognitive impairment, Parkinson's disease (PD), multiple sclerosis (MS), traumatic brain injury (TBI), or Fragile X-associated tremor/ataxia syndrome.

A "neurological disorder," as used herein, refers to a disorder of the nervous system, for example, the central nervous system (CNS). Examples of neurological disorders include, without limitation,

proteopathies (e.g., synucleinopathies, tauopathies, prion diseases, and amyloidosis (e.g., A β -amyloidosis) and/or neurodegenerative disorders (e.g., ApoE-associated neurodegenerative disorders).

It is to be understood that the above lists are not all-inclusive, and that a disorder or disease may fall within various categories. For example, Alzheimer's disease can be considered a neurodegenerative disease, a proteopathy, and, in some instances, may also be considered a synucleinopathy. Likewise, Parkinson's disease can be considered a neurodegenerative disease and a proteopathy.

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient.

Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). For example pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate,

cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

A "proteopathy" is a disorder that is characterized by structural abnormalities of proteins (e.g., protein misfolding and/or protein aggregation) that disrupt the function of cells, tissues, and/or organs of a subject. In some cases, misfolding can lead to loss of a protein's usual function. In other cases, a misfolded protein can gain toxic functions. In some cases, proteins can be induced to have structural abnormalities by exposure to the same (or a similar) protein that has folded into a disease-causing conformation (e.g., amyloid beta, tau, alpha-synuclein, superoxide dismutase-1 (SOD-1), polyglutamine, prion, and TAR DNA-binding protein-43 (TDP-43)). Exemplary, non-limiting proteopathies include AD, Parkinson's disease, Alexander disease, amyotrophic lateral sclerosis (ALS), a prion disease (e.g., Creutzfeldt-Jakob disease), Huntington's disease, Machado-Joseph disease, Pick's disease, or frontotemporal dementia.

By a "reference" is meant any useful reference used to compare protein or mRNA levels related to neurological disorders. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A "reference sample" can be, for example, a control, e.g., a predetermined negative control value such as a "normal control" or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having neurological disorders; a sample from a subject that is diagnosed with cardiac artery aneurysms or stenosis; a sample from a subject that has been treated for neurological disorders; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By "reference standard or level" is meant a value or number derived from a reference sample. A "normal control value" is a predetermined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range ("between X and Y"), a high threshold ("no higher than X"), or a low threshold ("no lower than X"). A subject having a measured value within the normal control value for a particular biomarker is typically referred to as "within normal limits" for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a neurological disorder. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

As used herein, the term "subject" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or

therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

5 A "synucleinopathy" is a disorder characterized by misfolding and/or abnormal accumulation of aggregates of alpha-synuclein in the central nervous system (e.g., in neurons or glial cells). Exemplary, non-limiting synucleinopathies include Parkinson's disease (PD), dementia with Lewy bodies, pure autonomic failure, multiple system atrophy, incidental Lewy body disease, pantothenate kinase-associated neurodegeneration, Alzheimer's disease, Down's Syndrome, Gaucher disease, or the
10 Parkinsonism-dementia complex of Guam.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment
15 of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes
20 eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

Brief Description of the Drawings

The application file contains at least one drawing executed in color. Copies of this patent or
25 patent application with color drawings will be provided by the Office upon request and payment of the necessary fee.

FIGS. 1A and 1B are graphs showing that growth inhibition of by 1,2,4-oxadiazoles occurs through same mechanism as the rescue of toxicity in the apolipoprotein E4 (ApoE4) Alzheimer's disease yeast model. (**Fig. 1A**) Compound 1, a representative 1,2,4-oxadiazole, was profiled in ApoE4 (top) and
30 control (bottom) non-inducing conditions at 12-point dose (x-axis). The Y-axis shows raw OD₆₀₀. Compound 1 exhibited a bell-shaped dose-response curve (DRC) in the ApoE4 model. Rescue decreased at concentrations just above the maximal efficacy (Emax). In the control condition (bottom panel), growth decreased at this same concentration. (**Fig. 1B**) The relationship between Emax (rescue in ApoE4) and growth inhibition (in the control condition) correlated across 34 tested 1,2,4-oxadiazoles.
35 The maximal rescue dose (EC100) is shown on the y-axis for ApoE4 and minimal inhibitory dose (IC100) in the control condition is shown on the x-axis. This correlation indicates that growth inhibition is caused by the same on-target activity that rescues ApoE4 toxicity.

FIGS. 2A and 2B are graphs showing that exogenous oleic acid reverses growth inhibition and model rescue by Ole1/SCD-targeting 1,2,4-oxadiazoles. Growth was measured by reading OD₆₀₀ in a
40 microplate reader and normalized to solvent control DMSO samples. (**Fig. 2A**) Growth inhibition (24 h) of strain GM *yap1 flr1* by Ole1/SCD-targeting 1,2,4-oxadiazoles is reversed by exogenous 0.5 mM

oleic/palmitoleic acid, which did not affect growth inhibition by other compounds (black dots indicate other scaffolds tested). Maximal growth inhibition across a dose range from 33 nM to 33 μ M is plotted. (Fig. 2B) Rescue (40 h) of the yeast alpha-synuclein ("aSyn") model by 1,2,4-oxadiazoles was reversed by exogenous 0.5 mM oleic/palmitoleic acid, which did not affect rescue by other scaffolds. Maximal model rescue across a dose range from 33 nM to 33 μ M is plotted.

FIGS. 3A and 3B are graphs showing that point mutations in yeast *OLE1* confer resistance to growth inhibition and alpha-synuclein model rescue by 1,2,4-oxadiazoles. Growth was measured by reading OD₆₀₀ in a microplate reader. (Fig. 3A) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in complete synthetic medium (CSM)-glucose media at the indicated doses of 1,2,4-oxadiazole Compound 2 for 24 h. Growth was normalized to samples treated with the solvent control dimethyl sulfoxide (DMSO), set as "1". (Fig. 3B) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (Wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in CSM-galactose media (inducing expression of alpha-Synuclein) at the indicated doses of the 1,2,4-oxadiazole Compound 2 for 40 h. Growth was normalized to samples treated with the solvent control DMSO, where rescue is set as "1".

FIG. 4 is a graph showing that a *ole1Δ* deletion mutant is resistant to the growth-inhibitory effects of 1,2,4-oxadiazoles, but not other compounds. Twenty-four hour growth (presented as raw OD₆₀₀) of the *ole1Δ* deletion strain in yeast extract-peptone-dextrose (YPD) media is shown, with drugs added at the indicated concentrations.

FIG. 5 is a graph showing that reducing *OLE1* expression by deleting *MGA2* rescues the growth of the ApoE4 yeast model. Yeast cells expressing ApoE4 were deleted for the *MGA2* gene and their growth was assessed over time (compared to their isogenic, *MGA2* wild-type counterpart). Growth was assessed by OD₆₀₀. Where indicated, 0.08 or 0.32 mM of oleic and palmitoleic acids (each) as added to the growth media in 0.01% tween (final).

FIG. 6 is a series of graphs showing that commercial Scd inhibitors target human SCD1/SCD5 in yeast. Yeast surviving solely on yeast *OLE1*, or human SCD1 or SCD5, were treated with four commercial Scd inhibitors at indicated concentrations. Data are expressed as a percent of the DMSO-treated condition. All four compounds potently reduced growth of both SCD1-expressing yeast and SCD5-expressing yeast, but not the strain expressing Ole1. This growth inhibition was reversed by oleic/palmitoleic acid competition, similar to the results shown in Figs. 2A and 2B.

FIG. 7 is a series of graphs showing that 1,2,4-oxadiazoles target human SCD1 and SCD5. Three "SCD" strains expressing yeast *OLE1* or human SCD1 or SCD5 were treated with five representative 1,2,4-oxadiazoles and a cycloheximide toxicity control at concentrations indicated on the log₁₀ x-axis. The y-axis indicates the percent of the DMSO-treated condition. All of the 1,2,4-oxadiazole compounds potently inhibited Ole1-expressing yeast and showed variable growth inhibition of the SCD1 or SCD5 yeast strains. These data confirm that 1,2,4-oxadiazoles target the human protein and link Scd inhibition to rescue of neurodegenerative disease models. Approximately one half of all (250) 1,2,4-oxadiazoles tested inhibited SCD1 or SCD5 in a manner that was reversed by oleic/palmitoleic acid treatment. Cyclohexamide, a translation inhibitor (top left panel), inhibited growth of all three strains with the same potency, indicating differences in growth inhibition was due to targeting the human protein.

FIGS. 8A-8D are graphs showing that treatment of yeast cells with the 1,2,4-oxadiazole Compound 2 inhibits lipid desaturation. Exponentially-growing wild-type yeast cells were treated with the indicated doses of the 1,2,4-oxadiazole Compound 2 for the indicated times before cellular lysis, lipid extraction, and analysis by global LC-MS/MS profiling. The relative abundance (fraction of total cellular lipid signal) after 1.5 h and 8 h of the most abundant saturated lipid, phosphatidylcholine 26:0, is depicted in Figs. 8A and 8B, respectively. The relative abundance after 1.5 h and 8 h drug treatment of the most abundant lipid with 2 or more degrees of unsaturation, phosphatidylcholine 16:1; 18:1, is depicted in Figs. 8C and 8D, respectively. The data indicate a >300-fold increase in the abundance of the saturated lipid phosphatidylcholine 26:0 after 8 h treatment with Compound 2, and a >12-fold decrease in the abundance of the unsaturated lipid phosphatidylcholine 16:1, 18:1, indicating that Compound 2 blocks cellular fatty acid desaturase activity (Ole1 is the only fatty acid desaturase in yeast).

FIG. 9 shows *OLE1* mutations conferring resistance to growth inhibition to 1,2,4-oxadiazoles identified by genome sequencing of resistant mutants. Cells were plated on media containing 10 μ M of the 1,2,4-oxadiazole Compound 3 and resistant colonies that emerged were isolated, and genomic DNA was prepared from mutants and the parental, drug-sensitive control strain. Genomic DNA sequence was aligned to the *Saccharomyces cerevisiae* reference and unique mutations in the 1,2,4-oxadiazole-resistant mutants were identified. The position of the mutations, the amino acid changes they encode, and the fold resistance (increase in minimal inhibitory concentration) of Compound 3 are shown.

FIG. 10 is a graph showing that Rab1 co-expression in U2OS cells rescues alpha-synuclein-dependent decreases in cellular ATP levels. U2OS cells were transfected with no plasmid (Mock), 2 μ g of empty plasmid control (pcDNA) or 2 μ g alpha-synuclein (ASYN). U2OS cells were also co-transfected with 2 μ g alpha-synuclein in combination with 0.5 or 0.25 μ g of mammalian Rab1a (mRab1a). ATP levels were normalized across all samples setting the Mock control as 100%. Bars depict mean values of triplicate determinations; error bars indicate standard deviation. One-way analysis of variance (ANOVA) was utilized to evaluate differences between pcDNA alone, alpha-synuclein alone, or alpha-synuclein in combination with mRab1a, with Bonferroni post-test to adjust for multiple comparisons (** p 0.001, **** p 0.0001).

FIGS. 11A and 11B are graphs showing that U2OS cells and induced pluripotent stem cell (iPSC)-derived human neurons expressed SCD1 and SCD5. (**Fig. 11A**) Total RNA was extracted from differentiated human neurons derived from iPSC cells obtained from a patient with alpha-synuclein gene triplication (S3), U2OS cells and rat PC-12 cells. Quantitative reverse transcription-polymerase chain reaction (RT-PCR) was performed to quantify mRNA levels of human SCD1 (hSCD1) and human SCD5 (hSCD5). All samples were normalized to hSCD1 level in U2OS cells, which was set to 1.0. Bars depict mean values of triplicate determinations; error bars indicate standard deviation. (**Fig. 11B**) Analysis of SCD1 protein levels in S3 neurons and U2OS cells. Protein extracts from S3 and U2OS cells were analyzed by immunoblotting with an antibody specific for human SCD1. Duplicate immunoblots were probed with an antibody against β -tubulin as a loading control.

FIGS. 12A and 12B show that knocking down SCD5 expression with siRNA rescues alpha-synuclein toxicity in U2OS cells. U2OS cells were transfected with empty vector control ("pcDNA") or alpha-synuclein (" α -synuclein/pcDNA") in combination with a scrambled (SCR) siRNA control (50 nM), or human SCD5 siRNA (10, 25 or 50 nM). (**Fig. 12A**) Cellular health was assessed 48 h after transfection by

evaluating ATP levels. Cell toxicity in the alpha-synuclein plus SCR siRNA was set as the floor of the assay, and then all samples were normalized to pcDNA with SCD5 siRNA (set to 100%) to calculate the normalized percent rescue. Bars depict mean values of triplicate determinations; error bars indicate standard deviation. A two-tailed t-test was used to compare control conditions with SCR or SCD5 siRNA (* $p < 0.05$). Cells transfected with alpha-synuclein were analyzed together by ANOVA with Dunnett's post-test to correct for multiple comparisons (** $p < 0.01$, **** $p < 0.0001$). Significance is shown for the comparison of each alpha-synuclein plus SCD5 siRNA concentration compared against the alpha-synuclein plus SCR control. (Fig. 12B) Quantitative RT-PCR was utilized to confirm the levels of SCD5 mRNA. Values shown are the fold change in SCD5 mRNA levels relative to the SCR controls at 24 hours.

FIG. 13 is a graph showing that SCD inhibition with CAY10566 rescued alpha-synuclein-dependent decreases in cellular ATP levels. U2OS cells were transfected with alpha-synuclein, then treated with DMSO as a control (ASYN) or a titration of the commercially available SCD inhibitor CAY10566. Cellular ATP levels were assessed 72 h after transfection/treatment. ATP levels were normalized to the DMSO control which was set to 100%. Bars depict mean values of triplicate determinations; error bars indicate standard deviation. One-way ANOVA was utilized to evaluate CAY10566 treatment effects compared to DMSO controls, with Bonferroni post-test to adjust for multiple comparisons (* $p < 0.05$, ** $p < 0.01$).

FIG. 14 is a graph showing that SCD inhibition with CAY10566 reduced alpha-synuclein (A53T)-dependent neurite degeneration in transfected rat cortical neurons. Primary cultures of rat cortical neurons were co-transfected with a fluorescence reporter plasmid encoding RFP (neurite tracer) and control plasmid (empty) or plasmid containing alpha-synuclein with an A53T mutation, and treated with vehicle (DMSO) or a titration of CAY10566 ranging from 10 nM down to 10 pM as indicated. Neurite length was tracked by RFP signal every 6 h for 7 d. To follow the degeneration phase, neurite lengths were normalized to the peak neurite length for each condition and plotted over the subsequent (up to) 120 h.

FIG. 15 is a graph showing that SCD inhibition with CAY10566 reduced the cumulative risk of death in human iPSC-derived neurons harboring the alpha-synuclein A53T mutation. Human iPSC cells harboring the alpha-synuclein A53T mutation or an isogenic control line in which the mutation was corrected to wild-type were trans-differentiated into neurons. Single cells were evaluated for survival (based on overall morphology) over the course of the 192 hour study. Cell survival data was analyzed by a non-parametric Kaplan-Meier procedure to estimate survival probability, which is shown as the cumulative risk of cell death. (HR, hazard ratio; P , p value (* < 0.05 , ns=not significant (>0.05)); CI, confidence interval; N, number of neurons tracked).

FIG. 16 is a graph illustrating that non-selective SCD reference inhibitor, CAY10566, reduces risk of death in A53T α -synuclein transfected human iPSC-derived neurons. Human iPSC-derived neurons were co-transfected with a fluorescence reporter plasmid encoding RFP (morphology tracer) and control plasmid (empty) or plasmid containing α -synuclein-A53T mutation (syn-A53T). Neuron groups as indicated were treated with either DMSO or CAY10566 at the indicated doses. The lifetimes of single neurons were tracked over time based on either loss of RFP fluorescence signal or morphological indicators of neuron death such as loss of neurites or cell blebbing. Kaplan-Meier survival analysis was

used to generate cumulative risk of death plots. The cumulative risk of neuron death is plotted against time (hrs) for each group as indicated. CAY10566 treatment of the α -synuclein-A53T neurons was protective at each of the doses tested. Cox proportional hazard analysis was used to estimate relative risk of death, or hazard ratio (HR) and the P value was determined by the logrank test. CI, confidence interval; N, number of neurons.

FIG. 17 is a graph illustrating that an SCD5-selective inhibitor reduces risk of death in A53T α -synuclein transfected human iPSC-derived neurons. Human iPSC-derived neurons were co-transfected with a fluorescence reporter plasmid encoding RFP (morphology tracer) and control plasmid (empty) or plasmid containing α -synuclein-A53T mutation (syn-A53T). Neuron groups as indicated were treated with either DMSO or SCD5 Selective Inhibitor 1 ("SCD5-SI-1") at the indicated doses. The lifetimes of single neurons were tracked over time based on either loss of RFP fluorescence signal or morphological indicators of neuron death such as loss of neurites or cell blebbing. Kaplan-Meier survival analysis was used to generate cumulative risk of death plots. The cumulative risk of neuron death is plotted against time (hrs) for each group as indicated. SCD5 Selective Inhibitor 1 treatment of the α -synuclein-A53T neurons was protective at each of the doses tested. Cox proportional hazard analysis was used to estimate relative risk of death, or hazard ratio (HR) and the P value was determined by the logrank test. CI, confidence interval; N, number of neurons.

FIG. 18A-18F are a series of graphs showing an evaluation of fatty acid saturation in guinea pig brain after oral administration of SCD inhibitors. Guinea pigs were dosed orally with SCD inhibitors twice daily (every 12 hours) for 5 days. Guinea pigs were dosed with vehicle, SCD5 Selective Inhibitor 1 ("SCD5-SI-1"), SCD5 Selective Inhibitor 2 ("SCD5-SI-2"), CAY10566 ("CAY") or SCD1/SCD5 Inhibitor 1 ("SCD1/5-1"), all compounds at 25 mg/kg with a volume-matched vehicle control. Four hours after the last dose on day 5, guinea pigs were sacrificed, and brains were removed after whole-body saline perfusion. Brains were homogenized, and fatty acids hydrolyzed from esterified lipids, which were then methylated to generate fatty acid methyl esters (FAME). Samples were evaluated on a gas chromatograph with a flame ionization detector (GC-FID) to quantify a comprehensive panel of fatty acid species. Brain samples were evaluated for levels of 16 (Fig. 18A) and 18 (Fig. 18B) carbon-containing fatty acids (C16, C18 respectively), and the desaturation index (DI) was calculated by taking the ratio of desaturated to saturated fatty acid for each species. SCD5-selective compounds SCD5-SI-1 and SCD5-SI-2, and SCD non-selective inhibitors CAY10566 and SCD1/5-1, all decreased the C16 DI, indicating they were active in modulating SCD activity in the brain and promoting a pharmacodynamic response. No significant changes were observed in the C18 DI. Brain samples were evaluated for the relative levels of the positional isomers of C16, including C16:1n7 palmitoleic acid (Fig. 18C) or C16:1n9 monounsaturated fatty acids (Fig. 18D). C16:1n9 fatty acids are derived from monounsaturated C18:1n9 fatty acids that have lost 2 carbon units due to β -oxidation. Compared to vehicle controls, all compounds decreased the levels of monounsaturated C16:1 fatty acids. Figures 18E and 18F show evaluation of brain samples for the relative levels of linoleic acid (18:2n6) (Fig. 18E) and gamma-linoleic acid (18:3n6) (Fig. 18F). Both species are essential omega-6 fatty acids, and both significantly increased with administration of SCD5-selective or non-selective compounds. n = 8 for each group. Individual points plotted, mean indicated by black bars. Error bars represent standard deviation. Data was analyzed by one-way ANOVA with Tukey's post-hoc test to account for multiple comparisons. ** p < 0.01, *** p <

0.005, **** $p < 0.0001$. Upper black bars across graph and corresponding black significance marks indicate comparison to vehicle controls. Lower bars across graph and corresponding significance marks indicate comparison between the compound-treated groups. Non-significant changes/comparisons are indicated (n.s.).

5

Detailed Description of the Invention

The present disclosure provides methods for the treatment of neurological disorders, e.g., by suppressing toxicity in cells related to protein misfolding and/or aggregation.

10 SCD Inhibitors

SCD inhibitors include any compound described herein such as a compound of any one of Formula I-LXI, or pharmaceutically acceptable salts thereof.

A number of approaches are known in the art for determining whether a compound modulates expression or activity of SCD, for example, to determine whether a compound is an SCD inhibitor (e.g.,
15 an SCD1 inhibitor and/or an SCD5 inhibitor), and any suitable approach can be used in the context of the invention. The SCD activity assay may be cell-based, cell-extract-based (e.g., a microsomal assay), a cell-free assay (e.g., a transcriptional assay), or make use of substantially purified proteins. For example, identification of compounds as SCD inhibitors can be performed using an SCD liver microsomal assay, for example, as described by Shanklin et al. *Proc. Natl. Acad. Sci. USA* 88:2510-2514, 1991 or Miyazaki et
20 al. *J. Biol. Chem.* 275:30132-30138, 2000. In some instances, liquid-chromatography/mass spectrometry (LC/MS)-based approaches can be used to measure SCD activity, for example, as described by Dillon et al. *Anal. Chim. Acta.* 627(1):99-104, 2008. A high-throughput assay can be used, for example, as described by Soulard et al. *Anal. Chim. Acta.* 627(1):105-111, 2008. Still further approaches to measure SCD activity are described in U.S. Patent No. 7,790,408.

25 Any suitable method can be used to determine whether a compound binds to SCD (e.g., SCD1 and/or SCD5), for instance, mass spectrometry, surface plasmon resonance (SPR), or immunoassays (e.g., immunoprecipitation or enzyme-linked immunosorbent assay).

Any suitable method can be used to determine whether a compound modulates expression of SCD (e.g., SCD1 and/or SCD5), for instance, Northern blotting, Western blotting, RT-PCR, mass
30 spectrometry, or RNA sequencing.

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to inhibit toxicity caused by
35 protein misfolding and/or aggregation, e.g., α -synuclein misfolding and/or aggregation, in a cell.

Another aspect of the present invention relates to methods of treating and/or preventing a neurological disorders such as neurodegenerative diseases in a subject in need thereof. The pathology of neurodegenerative disease, may be characterized by the presence of inclusion bodies in brain tissue of affected patients.

40 In certain embodiments, neurological disorders that may be treated and/or prevented by the inventive methods include, but are not limited to, Alexander disease, Alpers' disease, AD, amyotrophic

lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, Steele-Richardson-Olszewski disease, tabes dorsalis, and Guillain-Barre Syndrome.

Combination Formulations and Uses Thereof

The compounds of the invention can be combined with one or more therapeutic agents. In particular, the therapeutic agent can be one that treats or prophylactically treats any neurological disorder described herein.

Combination Therapies

A compound of the invention can be used alone or in combination with other agents that treat neurological disorders or symptoms associated therewith, or in combination with other types of treatment to treat, prevent, and/or reduce the risk of any neurological disorders. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6, 2005). In this case, dosages of the compounds when combined should provide a therapeutic effect.

Pharmaceutical Compositions

The compounds of the invention are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*. Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a suitable diluent, carrier, or excipient.

The compounds of the invention may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the scope of the invention. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the invention may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound of the invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic

administration, a compound of the invention may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers.

A compound of the invention may also be administered parenterally. Solutions of a compound of the invention can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose.

5 Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003, 20th ed.) and in The United States Pharmacopeia: The
10 National Formulary (USP 24 NF19), published in 1999.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

15 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device,
20 such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles,
25 where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter.

The compounds of the invention may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is
30 determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

The dosage of the compounds of the invention, and/or compositions comprising a compound of
35 the invention, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds of the invention may be administered
40 initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds of the invention are administered to a

human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered. Preferred dose ranges include, for example, between 0.05-15 mg/kg or
 5 between 0.5-15 mg/kg.

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-50 mg/kg (e.g., 0.25-25 mg/kg). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20
 10 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

EXAMPLES

Example 1: Stearoyl-CoA Desaturase (SCD) is the Target of 1,2,4-oxadiazoles, and SCD Inhibition Rescues Alpha-Synuclein and ApoE4-Dependent Toxicity in Yeast Disease Models

15 A. Materials and Methods

Strain Construction and OLE1 Replacement with SCD1 or SCD5

Strain GMYF was constructed from the ABC16/Green monster strain described in Suzuki et al. *Nat. Methods* 8(2):159-164, 2011. In this strain, *YAP1* was deleted using a HIS3-MX6 cassette, and *FLR1* was deleted using a NAT-MX6 cassette using standard methods. The knockout cassettes were
 20 PCR-amplified from plasmid templates (see, e.g., Bahler et al. *Yeast* 14(10):943-951, 1998; Longtine et al. *Yeast* 14(10):953-961, 1998) and transformed into yeast using lithium acetate-based transformation (Gietz et al. *Methods Mol. Biol.* 1205:1-12, 2014). The *yap1::his3* deletion strain was selected on media lacking histidine and *flr1::NAT* on plates containing 100 µg/mL nourseothricin. All strains were confirmed by diagnostic PCR. Strain W303 *pdr1Δ pdr3Δ* was constructed from W303-1A (American Type Culture
 25 Collection (ATCC) 208352) by deleting *PDR1* and *PDR3* with kan-MX6 cassettes separately in MATa and MATα W303a isolates, mating, sporulating, and identifying the double deletion haploids by tetrad dissection and identification of non-parental ditype tetrads. Strain W-erg3 was derived from W303 *pdr1Δ pdr3Δ* by deleting *SNQ2* with NAT-MX6, *YAP1* with HIS3-MX6, and *ERG3* with BleMX.

Strain ApoE-*mga2Δ* was generated by amplifying 1000 base pairs (bp) upstream and
 30 downstream of the *MGA2* ORF in a strain in which *MGA2* was deleted using a G418 (GENETICIN®) resistance cassette (kanMX) (Piotrowski et al. *Proc. Natl. Acad. Sci. USA* 112(12):E1490-1497, 2015) and transforming the resulting deletion cassette into the ApoE4 strain in the BY4741 (ATCC 201388) genetic background. The ApoE strain is described, for example, in International Patent Application Publication No. WO 2016/040794, which is incorporated herein by reference in its entirety.

The alpha-synuclein expression strain was made in the same manner as described in Su et al. *Dis. Model Mech.* 3(3-4):194-208, 2010, except that the alpha-synuclein construct lacked the green
 35 fluorescent protein (GFP) tag.

Strain *ole1Δ* (yeast *ole1* deletion mutant) was constructed by deleting *OLE1* with NAT-MX6 in BY4741, amplifying the deletion cassette from the genomic DNA of the resulting strain with primers
 40 flanking the ORF by 1000 bp upstream and downstream, transforming the resulting deletion cassette into

W303 *pdr1Δ pdr3Δ*, and plating transformants on YPD media containing G418 (200 µg/mL) and nourseothricin (100 µg/mL) with 0.01% TWEEN®-20 and 0.5 mM oleic and palmitoleic acids.

To generate yeast strains expressing SCD1 or SCD5 as the sole desaturase, the human SCD1 and SCD5 genes were cloned from cDNAs (Harvard PlasmID database Clone ID HsCD00340237 for SCD1 and HsCD00342695 for SCD5) into yeast plasmid pRS316 (ATCC 77145) between the yeast *TDH3* promoter and the *CYC1* terminator. The coding sequence of yeast *OLE1* was also cloned into this plasmid. These clones were then transformed into the *ole1Δ* strain and plated on CSM-Ura media (CSM lacking uracil) with 2% glucose (w/v) and independent colonies were isolated and amplified.

Compound Profiling Methods

All compound profiling experiments were performed using the same basic protocol. Different genetic backgrounds (e.g., gene deletions) or conditions (e.g., addition of oleic and palmitoleic acid) were replaced as indicated below.

Yeast were cultured using standard techniques in complete synthetic media (CSM) and yeast nitrogen base supplemented with 2% (w/v) carbon source (glucose, raffinose, or galactose) to regulate the expression of the toxic disease protein. An initial starter culture was inoculated in 3 mL CSM-Glucose media and incubated overnight in a 30°C shaker incubator (225 rpm). Saturated morning cultures were then diluted 1:20 in fresh CSM-Raffinose media and grown for 6 h to an OD₆₀₀ (optical density) of ~0.4-0.8 at 30°C with shaking.

Compound stocks (10 mM in 100% DMSO) were arrayed into 384 round well, v-bottom polypropylene plates and diluted according to indicated dilution factors. Compound administration was performed in two separate steps. First, 15 µL of CSM-Galactose (induces expression of toxic protein) was dispensed into clear 384 well assay plates using a MULTIDROP™ Combi reagent dispenser. The diluted compound stock plates were then applied to the assay plates using an automated workstation (Perkin Elmer JANUS™) outfitted with a 384 pin tool containing slotted pins that deliver 100 nL of compound. The cultures described above were then diluted to a 2x concentration (0.03 and 0.08 for alpha-synuclein and ApoE, final OD₆₀₀ of 0.015 and 0.04) in CSM-Galactose. For wild-type and *Ole1/SCD1/SCD5* plasmid-containing strains, the 2x cell density was 0.02. In all experiments, 15 µL culture was then dispensed into the pinned assay plate to achieve 30 µL of the 1x OD₆₀₀ culture and a top drug concentration of 33.3 µM. For 96-well assays (Figs. 1A and 1B), compound dilutions in DMSO were generated in 96 well plates and 1 µL was manually pipetted into 96 well clear bottom assay plates.

For experiments with oleic and palmitoleic acid supplementation (Figs. 2A, 2B, 4, and 5), TWEEN®-20 was first added to culture media at a concentration of 0.01%. Oleic and palmitoleic acid were both then added at the indicated concentrations (0.08 to 0.5 mM) and mixed thoroughly prior to compound pinning or the addition of yeast.

For experiments using a plasmid-borne copy of *Ole1*, *SCD1*, or *SCD5* (Figs. 3B, 6, and 7), media lacking uracil (SX-Ura, where X is glucose, raffinose, or galactose), was used for all steps of the compound profiling protocol to ensure its maintenance throughout the assay.

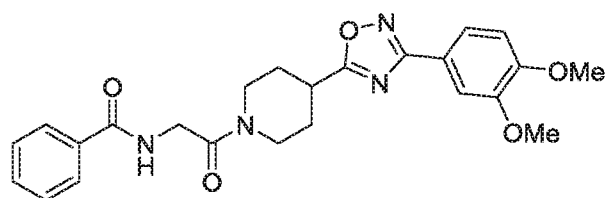
After yeast delivery, assay plates were incubated under humidified conditions at 30°C for 24 to 40 h. ApoE4 rescue experiments were stopped at 24 h, aSyn experiments at 40 h, *Ole1* at 24 h, and *SCD1/SCD5* at 40 h. The growth of yeast was monitored by reading the OD₆₀₀ of each well using a

microplate reader (Perkin Elmer EnVision™). Data were analyzed as follows. For model rescue experiments, raw data were processed by background subtracting and calculating a fold-change relative to DMSO control $[(\text{EXP}-0.035)/(\text{DMSO}-0.035) - \text{where } 0.035 \text{ is the } \text{OD}_{600} \text{ contributed by an empty well containing } 30 \mu\text{L} \text{ of media alone}]$. For growth inhibition of wild-type cells, raw data were processed by background subtracting and converting values to a percent of the nontreated condition for that strain $[(\text{EXP}-0.035)/(\text{DMSO}-0.035) \times 100\%]$.

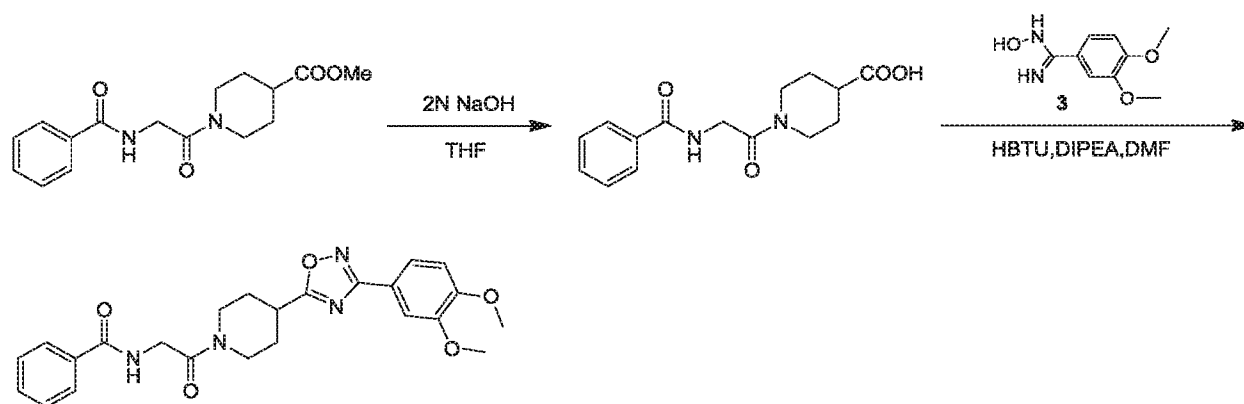
Compound Sources

Compounds were sourced as follows: cycloheximide (Sigma Aldrich), A939572 (Abcam), CAY10566 (Abcam), MF-438 (Calbiochem), MK-8245 (Selleckchem), oleic acid (Sigma Aldrich), palmitoleic acid (Acros organics), mycophenolic acid (Sigma Aldrich), and tunicamycin (Cayman Chemical).

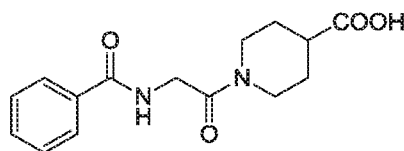
Compound 1 has the structure:



Compound 1 may be synthesized by methods known in the art. For example, as shown in the scheme below:



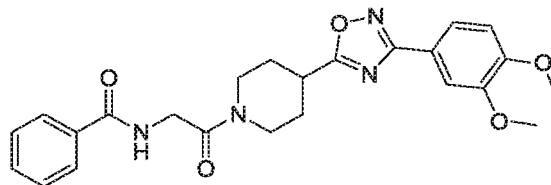
Step 1: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.0 g, 16.4 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 16.4 mL). The mixture was stirred at 20 °C for 2 h and then acidified by the addition of concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (3.25 g, 11.2 mmol, 68 %) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.87 (d, $J=7.5$ Hz, 2H), 7.59 - 7.42 (m,

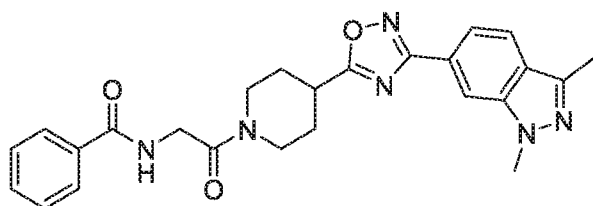
3H), 4.39 - 4.20 (m, 3H), 3.92 (d, $J=14.1$ Hz, 1H), 3.24 (t, $J=11.5$ Hz, 1H), 2.98 - 2.88 (m, 1H), 2.62 (s, 1H), 2.08 - 1.89 (m, 2H), 1.81 - 1.53 (m, 2H).

Step 2: Preparation of *N*-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

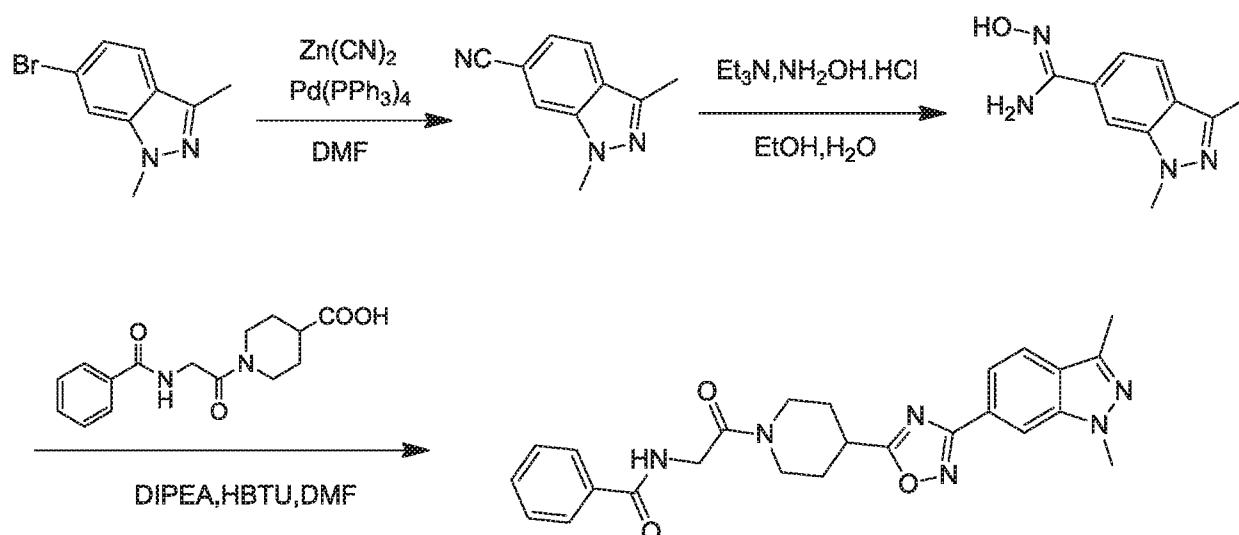


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (2.0 g, 6.89 mmol) in *N,N*-dimethylformamide (30 mL) was added *N*-hydroxy-3,4-dimethoxybenzimidamide (1.62 g, 8.27 mmol), *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (2.67 g, 20.67 mmol, 3.61 mL) and 1-bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (2.62 g, 6.89 mmol). The mixture was stirred at 20 °C for 2 h and then warmed at 120 °C for 2 h. The reaction mixture was quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 2) to give a yellow solid. The yellow solid was washed with ethyl acetate (30 mL), then the mixture was filtered, and the filter cake was dried in vacuo to give *N*-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (1.29 g, 2.86 mmol, 42 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, $J=8.9$ Hz, 1H), 4.58 - 4.47 (m, 1H), 4.32 (d, $J=3.9$ Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) $[M+H]^+ = 451.3$.

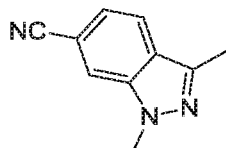
Compound 2 has the structure:



Compound 2 may be synthesized by methods known in the art. For example, Compound 2 may be synthesized as shown in the scheme below:

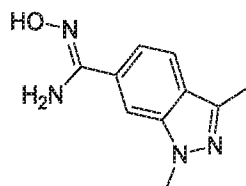


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



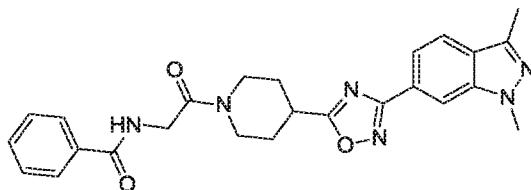
To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (400 mg, 1.78 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (209 mg, 1.78 mmol, 112 μ L) and tetrakis(triphenylphosphine)palladium(0) (205 mg, 178 μ mol, 0.10 eq) under nitrogen. The mixture was heated at 100 °C for 16 h, then cooled to 20 °C, water (10 mL) added, and the resulting mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated in vacuo to give crude product. Petroleum ether (40 mL) was added to the crude product, then the mixture was filtered, and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (250 mg, 1.46 mmol, 82 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.78 - 7.71 (m, 2H), 7.34 (dd, J=1.3, 8.3 Hz, 1H), 4.07 (s, 3H), 2.61 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



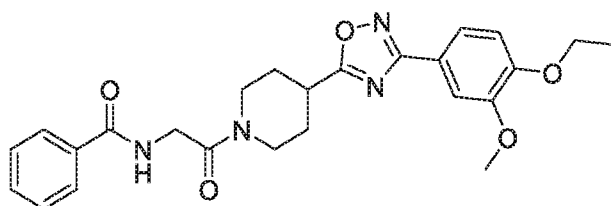
To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (100 mg, 584 μ mol) in ethanol (2 mL) was added hydroxylamine hydrochloride (81 mg, 1.17 mmol), triethylamine (118 mg, 1.17 mmol, 161 μ L) and water (200 μ L). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (5 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (140 mg) as a white solid. LCMS (ESI) m/z: [M+H]⁺ = 205.1.

Step 3: Preparation of *N*-(2-(4-(3-(1,3-dimethyl-1*H*-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

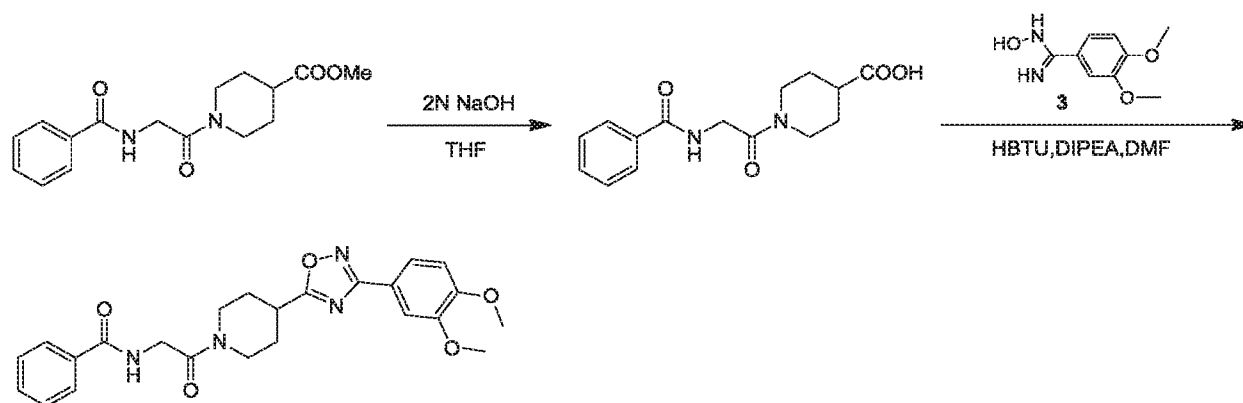


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 μ mol) in
 5 *N,N*-dimethylformamide (2 mL) was added (*Z*)-*N'*-hydroxy-1,3-dimethyl-1*H*-indazole-6-carboximidamide
 (101 mg, 496 μ mol), (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg,
 413 μ mol) and *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 μ L). The mixture was
 stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture cooled then purified directly
 by prep-HPLC (column: Waters Xbridge 150x2.5mm 5 μ m; mobile phase: [water (10mM ammonium
 10 carbonate)-acetonitrile]; B%: 30%-65%, 12 min) to give *N*-(2-(4-(3-(1,3-dimethyl-1*H*-indazol-6-yl)-1,2,4-
 oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (46 mg, 101 μ mol, 25 %) as a yellow solid. ¹H NMR
 (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.81 - 7.73 (m, 3H), 7.66 (dd, *J*=0.6, 8.4 Hz, 1H), 7.48 - 7.42 (m, 1H),
 7.42 - 7.35 (m, 2H), 7.26 (br. s., 1H), 4.46 (d, *J*=14.1 Hz, 1H), 4.24 (d, *J*=3.9 Hz, 2H), 4.01 (s, 3H), 3.86
 (d, *J*=13.7 Hz, 1H), 3.29 (ddd, *J*=3.6, 10.5, 14.2 Hz, 2H), 3.13 - 3.04 (m, 1H), 2.53 (s, 3H), 2.26 - 2.15 (m,
 15 2H), 2.04 - 1.89 (m, 2H); LCMS (ESI) *m/z*: [*M*+*H*]⁺ = 459.3.

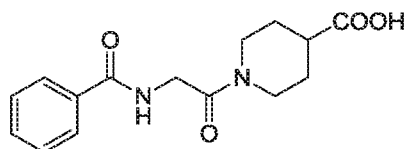
Compound 3 has the structure:



Compound 3 may be synthesized by methods known in the art. For example, Compound 3 may
 be synthesized as shown in the scheme below:

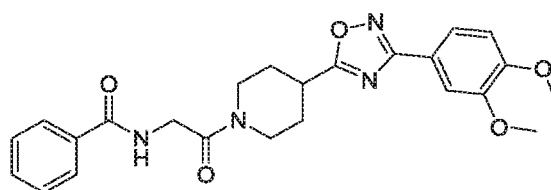


Step 1: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.0 g, 16.4 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 16.4 mL). The mixture was stirred at 20 °C for 2 h and then acidified by the addition of concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (3.25 g, 11.2 mmol, 68 %) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.87 (d, *J*=7.5 Hz, 2H), 7.59 - 7.42 (m, 3H), 4.39 - 4.20 (m, 3H), 3.92 (d, *J*=14.1 Hz, 1H), 3.24 (t, *J*=11.5 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.62 (s, 1H), 2.08 - 1.89 (m, 2H), 1.81 - 1.53 (m, 2H).

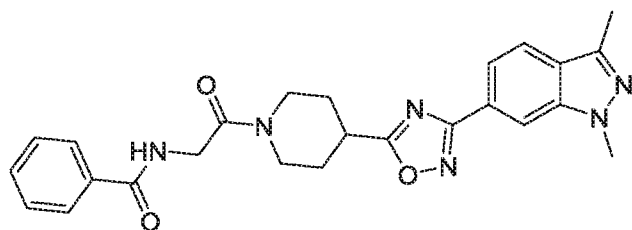
Step 2: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



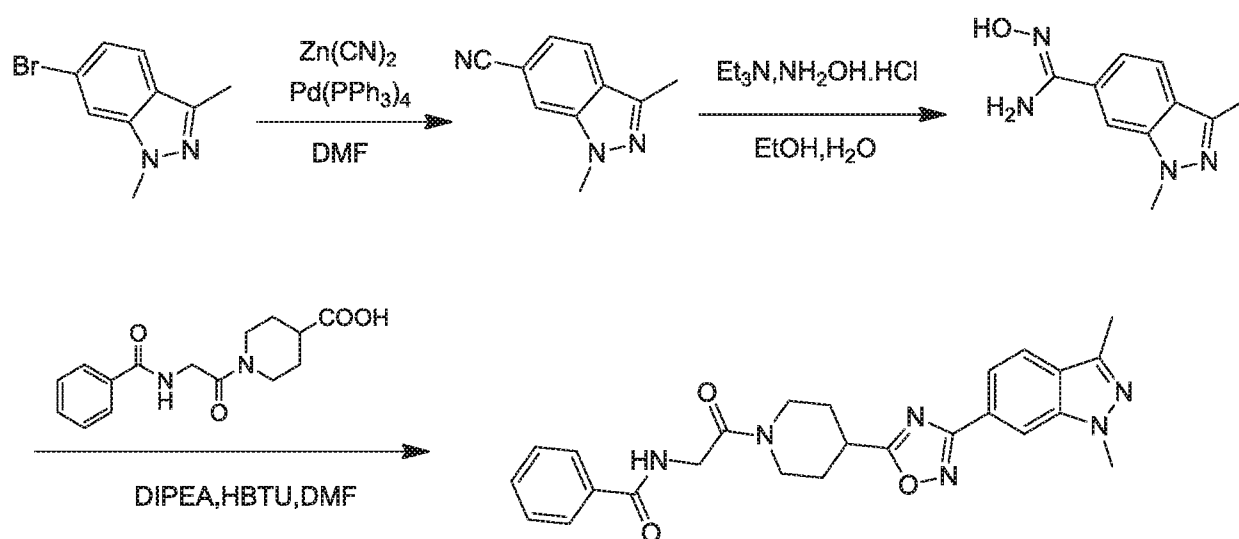
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (2.0 g, 6.89 mmol) in N,N-dimethylformamide (30 mL) was added N-hydroxy-3,4-dimethoxybenzimidamide (1.62 g, 8.27 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (2.67 g, 20.67 mmol, 3.61 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (2.62 g, 6.89 mmol). The mixture was stirred at 20 °C for 2 h and then warmed at 120 °C for 2 h. The reaction mixture was quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 2) to give a yellow solid. The yellow solid was washed with ethyl acetate (30 mL), then the mixture was filtered, and the filter cake was dried in vacuo to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (1.29 g, 2.86 mmol, 42 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, *J*=8.9 Hz, 1H),

4.58 - 4.47 (m, 1H), 4.32 (d, $J=3.9$ Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) $[M+H]^+ = 451.3$.

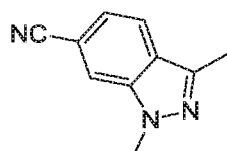
Compound 4 has the structure:



Compound 4 may be synthesized by methods known in the art. For example, Compound 4 may be synthesized as shown in the scheme below:

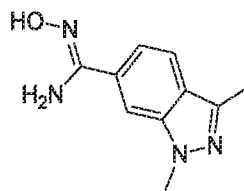


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



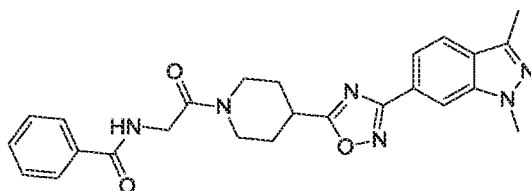
To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (400 mg, 1.78 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (209 mg, 1.78 mmol, 112 μ L) and tetrakis(triphenylphosphine)palladium(0) (205 mg, 178 μ mol, 0.10 eq) under nitrogen. The mixture was heated at 100 °C for 16 h, then cooled to 20 °C, water (10 mL) added, and the resulting mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated in vacuo to give crude product. Petroleum ether (40 mL) was added to the crude product, then the mixture was filtered, and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (250 mg, 1.46 mmol, 82 %) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.78 - 7.71 (m, 2H), 7.34 (dd, $J=1.3, 8.3$ Hz, 1H), 4.07 (s, 3H), 2.61 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (100 mg, 584 μ mol) in ethanol (2 mL) was added hydroxylamine hydrochloride (81 mg, 1.17 mmol), triethylamine (118 mg, 1.17 mmol, 161 μ L) and water (200 μ L). The mixture was heated at 75 $^{\circ}$ C for 2 h. After cooling to 20 $^{\circ}$ C, water (5 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (140 mg) as a white solid. LCMS (ESI) m/z: [M+H]⁺ = 205.1.

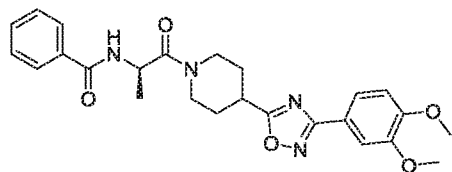
Step 3: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



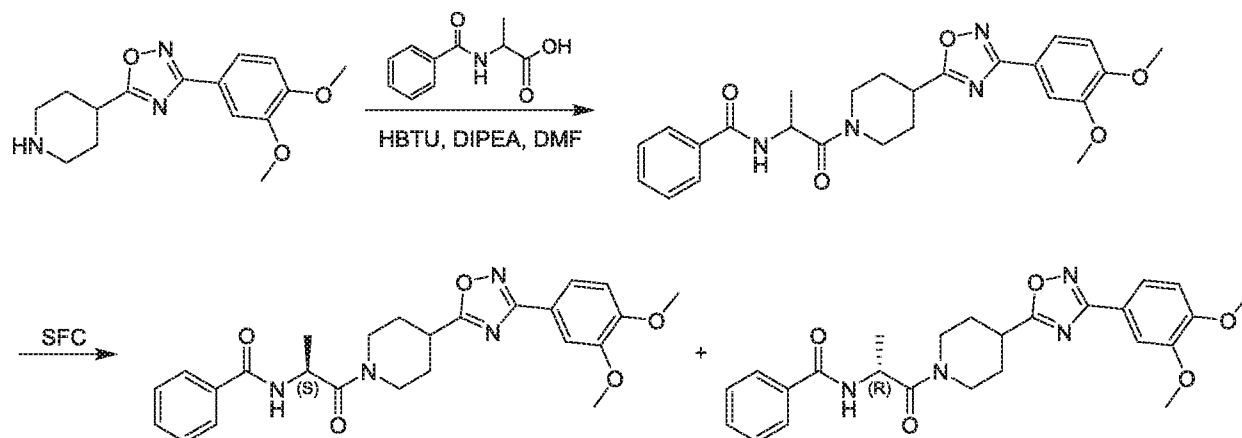
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 μ mol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (101 mg, 496 μ mol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 μ mol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 μ L). The mixture was stirred at 20 $^{\circ}$ C for 2 h, then heated at 120 $^{\circ}$ C for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5 μ m; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%, 12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (46 mg, 101 μ mol, 25 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.81 - 7.73 (m, 3H), 7.66 (dd, J=0.6, 8.4 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.35 (m, 2H), 7.26 (br. s., 1H), 4.46 (d, J=14.1 Hz, 1H), 4.24 (d, J=3.9 Hz, 2H), 4.01 (s, 3H), 3.86 (d, J=13.7

H_z, 1H), 3.29 (ddd, J=3.6, 10.5, 14.2 Hz, 2H), 3.13 - 3.04 (m, 1H), 2.53 (s, 3H), 2.26 - 2.15 (m, 2H), 2.04 - 1.89 (m, 2H); LCMS (ESI) m/z: [M+H]⁺ = 459.3.

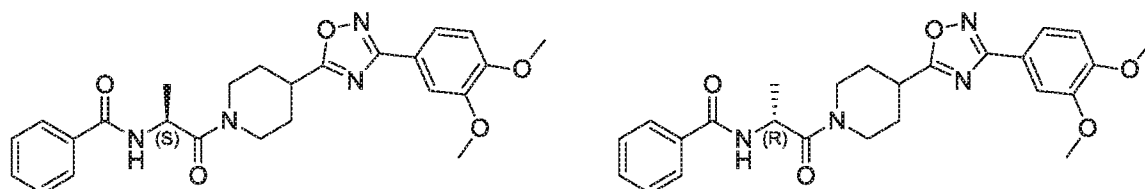
Compound 5 has the structure:



Compound 5 may be synthesized by methods known in the art. For example, Compound 5 may be synthesized as shown in the scheme below:



- 10 *Step 1: Preparation of N-[(R)-2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide and N-[(S)-2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide.*



- 15 To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 μ mol) and 2-benzamidopropanoic acid (105 mg, 544 μ mol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 μ mol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 μ L). The mixture was stirred at 20 °C for 5 h. The crude product was purified by prep-HPLC (column: Luna C18 150x25 5 μ m; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%, 12 min) to give rac-N-(1-(4-(3-(3,4-
- 20 (dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide then the product purified by SFC separation (column: AD(250x30mm, 5 μ m); mobile phase: [Neu-IPA]; B%: 42%-42%, min) to give N-2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1 (63 mg, 134.93 μ mol, 26 %) as a white solid and N-2-[4-[3-(3,4-

dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2 (56 mg, 120 μ mol, 23% as a white solid.

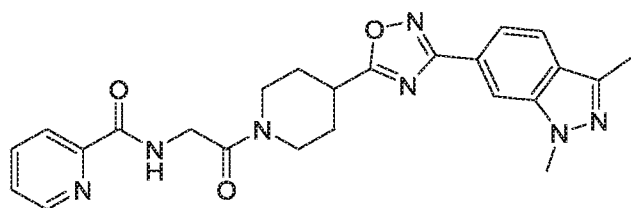
N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1:

^1H NMR (400MHz, DMSO- d_6) δ = 8.63 (br dd, J =7.3, 16.1 Hz, 1H), 7.88 (br d, J =7.5 Hz, 2H), 7.62 - 7.41 (m, 5H), 7.11 (br d, J =8.2 Hz, 1H), 4.97 (br d, J =6.4 Hz, 1H), 4.43 - 4.24 (m, 1H), 4.10 - 3.95 (m, 1H), 3.82 (s, 6H), 3.42 (br t, J =10.8 Hz, 1H), 3.30 - 3.21 (m, 1H), 2.99 - 2.83 (m, 1H), 2.09 (br d, J =11.9 Hz, 2H), 1.83 - 1.60 (m, 2H), 1.30 (br s, 3H); LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 465.3$. ee = 100%.

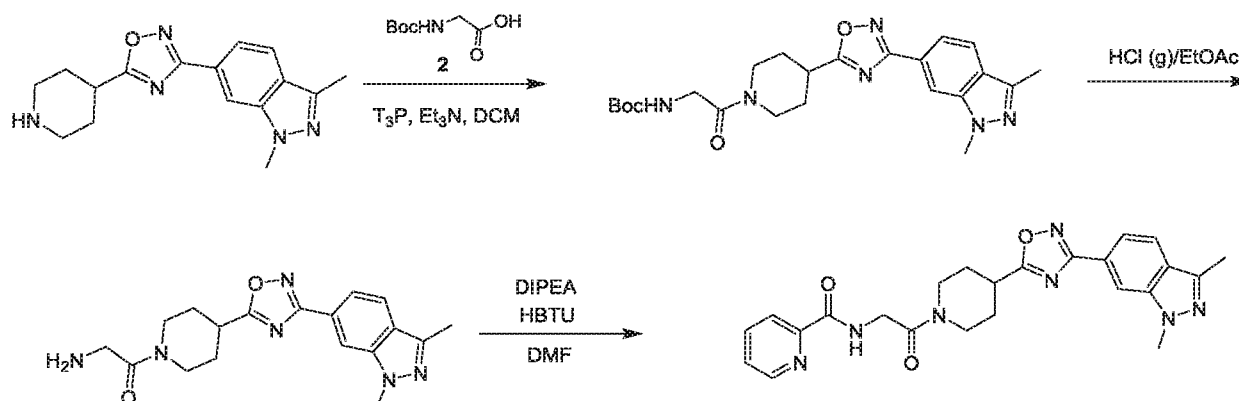
N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2:

^1H NMR (400MHz, DMSO- d_6) δ = 8.65 (br dd, J =7.6, 16.1 Hz, 1H), 7.98 - 7.86 (m, 2H), 7.70 - 7.41 (m, 5H), 7.13 (br d, J =8.2 Hz, 1H), 5.00 (br d, J =5.5 Hz, 1H), 4.49 - 4.24 (m, 1H), 4.12 - 3.96 (m, 1H), 3.85 (s, 6H), 3.45 (br t, J =10.7 Hz, 1H), 3.27 (br s, 1H), 3.05 - 2.83 (m, 1H), 2.12 (br d, J =12.5 Hz, 2H), 1.89 - 1.61 (m, 2H), 1.32 (br s, 3H); LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 465.3$. ee = 99.6

Compound 6 has the structure:

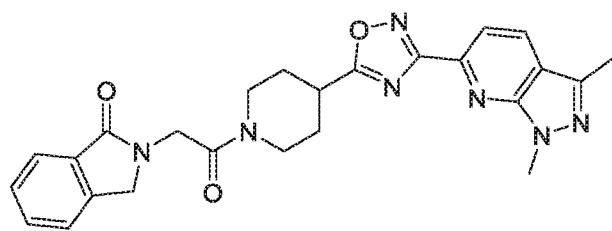


Compound 6 may be synthesized by methods known in the art. For example, Compound 6 may be synthesized as shown in the scheme below:

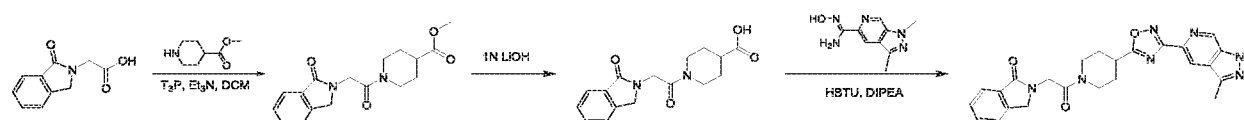


^1H NMR (400 MHz, CDCl_3) δ 8.93 (br s, 1H), 8.63 (d, J =4.0 Hz, 1H), 8.19 (d, J =7.7 Hz, 1H), 8.10 (s, 1H), 7.89 - 7.80 (m, 2H), 7.76 - 7.71 (m, 1H), 7.47 - 7.41 (m, 1H), 4.56 (br d, J =13.7 Hz, 1H), 4.35 (d, J =4.4 Hz, 2H), 4.09 (s, 3H), 3.96 (br d, J =13.9 Hz, 1H), 3.44 - 3.31 (m, 2H), 3.15 (br t, J =10.7 Hz, 1H), 2.60 (s, 3H), 2.34 - 2.23 (m, 2H), 2.11 - 1.95 (m, 2H); LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 460.2$.

Compound 7 has the structure:



Compound 7 may be synthesized by methods known in the art. For example, Compound 7 may be synthesized as shown in the scheme below:



¹H NMR (400MHz, CHLOROFORM-d) δ = 8.11 (d, J=8.4 Hz, 1H), 7.89 (d, J=8.2 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.47 - 7.41 (m, 2H), 4.60 - 4.41 (m, 5H), 4.16 (s, 3H), 4.12 - 4.05 (m, 1H), 3.41 - 3.31 (m, 2H), 3.06 - 2.98 (m, 1H), 2.62 - 2.57 (m, 3H), 2.25 (br t, J=14.6 Hz, 2H), 2.05 - 1.94 (m, 2H); LCMS(ESI) m/z: [M+H]⁺:472.3.

Drug Resistant Mutant Selection

Strains GMYF and W-erg3 were grown to saturation in CSM-glucose, centrifuged, resuspended in phosphate-buffered Saline (PBS), and plated at a density of 10⁷ cells/plate on solid 15cm petri dishes containing CSM with 2% galactose (w/v), 2% (w/v) agar, and 10 μ M Compound 3, and incubated at 30°C. Resistant colonies were isolated after 5-7 days, re-streaked on the same media, and resistance reconfirmed. Cultures of validated strains were then inoculated for genomic DNA isolation using a YeaStar™ yeast genomic DNA kit (Zymo Research).

Libraries were prepared for sequencing using the Illumina NEXTERA™ library prep kit and sequenced via Illumina HiSeq™ 2500 1X50 bp (single end reads). Sequences were aligned to the *S. cerevisiae* reference genome (S288CCR64-1-1, Saccharomyces Genome Database (SGD)) using Burrows-Wheeler Aligner (BWA, see, e.g., Li et al. *Bioinformatics* 25:1754-1760, 2009; Li et al. *Bioinformatics* 2010, Epub (PMID 20080505)). The BWA output SAI files were converted to SAM files using BWA. The SAM files were sorted using SAMtools 1.3.1 (Li et al. *Bioinformatics* 25:2079-2079, 2009). Variants (single-nucleotide polymorphisms (SNPs), indels) were identified using Freebayes (see, e.g., arXiv:1207.3907). Variant locations were summarized using snpEFF (Cingolani et al. *Fly* (Austin) 6(2):80-92, 2012).

Quantitative Lipid Profiling

Overnight cultures of yeast strain W303 *pdr1Δ pdr3Δ* were diluted into CSM media with 2% (w/v) raffinose, OD₆₀₀ 0.25, and grown for 4 h before resuspending at an OD₆₀₀ of 0.2 in CSM media with 2% (w/v) galactose and adding Compound 2 or DMSO at the indicated concentrations. Cells were grown for the indicated timepoints before centrifugation, washing once in PBS, and freezing pellets. Lipids were extracted from pellets by resuspending the pellets in 600 μ L methanol, 300 μ L water, and 400 μ L chloroform, followed by cell lysis by vortexing with glass beads for 1 min. Samples were then centrifuged at 10,000 x g for 10 min, and the bottom layer that formed (organic/lipids) was moved into a new tube and evaporated. Samples were then analyzed by LC/MS/MS using a Thermo Scientific Q Exactive™

Orbitrap™ coupled to a Dionex UltiMate® 3000 ultra-high performance liquid chromatography system, following the method described in Tafesse et al. *PLoS Pathog.* 11(10): e1005188, 2015.

B. Results

The effect of 1,2,4-oxadiazoles on cell growth was assessed in a control condition and in a yeast model for ApoE4 toxicity (see International Patent Application Publication No. WO 2016/040794). The control condition was growth of the ApoE4 strain under non-inducing conditions using raffinose as the carbon source. The 1,2,4-oxadiazoles exhibited a bell-shaped rescue curve in the ApoE4 model (Fig. 1A, top panel). At higher concentrations, these compounds inhibited the growth in the control condition (Fig. 1B, bottom panel). The potency of model rescue correlated well with the potency of growth inhibition across the entire series of 1,2,4-oxadiazoles tested (Fig. 1B). These relationships indicate that the growth inhibition arises from an “on-target” activity, i.e., over activation or inhibition of a target that results in slowed growth.

Drug-resistant mutants can be used to identify the target of the compounds, for example, by preventing or reducing drug binding, and therefore allowing growth under inhibitory doses of 1,2,4-oxadiazole concentrations. Twenty drug-resistant mutants were isolated, and the mutants were subjected to whole-genome sequencing in order to identify genetic lesions associated with the drug resistance. Surprisingly, all mutations identified in the drug resistant mutants localized to OLE1 (YGL055W), the sole stearyl-CoA desaturase (SCD; also referred to as Δ9-desaturase) in yeast (Fig. 9). The drug resistant mutants specifically conferred resistance to 1,2,4-oxadiazoles, but were not cross-resistant to other toxic compounds. The *ole1* mutations identified included indels and substitution mutations, including A305V, L118Δ, S190T, A305T, I301N, A91T, S190T, P123T, and E118Q. These mutations are relative to the wild-type OLE1 sequence provided below.

```
MPTSGTTIELIDQFPKDDSSASSGIVDEVDLTEANILATGLNKKAPRIVNGFGSLMGSKE
MVSVEFDKKGNEKKSNDRLLEKDNQEKKEAKTKIHISEQPWTLNNWHQHLNWLNMVLVC
GMPMIGWYFALSGKVPLHLNVFLFSVFYYAVGGVSITAGYHRLWSHRSYSAHWPLRLFYA
IFGCASVEGSAKWWGSHRIHRYTDTLRDPYDARRGLWYSHMGWMLLKPNPKYKARADI
TDMTDDWTIRFQHRHYILLMLLTAFVIPTLICGYFFNDYMGGLIYAGFIRVFEVIQQATFC
INSLAHYIGTQFPDDRTPRDNWITAIVTFGEGYHNFHHEFPTDYRNAIKWYQYDPTKVI
IYLTSLVGLAYDLKKFSQNAIEEALIQQEQQKINKKKAKINWGPVLTDLPMWDKQTFLLAK
SKENKGLVVISGIVHDVSGYISEHPGGETLIKTALGKDATKAFSGGVYRHSNAAQNVLAD
MRVAVIKESKNSAIRMASKRGEIYETGKFF (SEQ ID NO: 1)
```

These data strongly suggest that Ole1 is the target of 1,2,4-oxadiazoles. Additionally, addition of exogenous oleic acid reversed both growth inhibition of wild-type cells and rescue of toxicity in a yeast disease model of alpha-synuclein toxicity (Figs. 2A and 2B, respectively). Likewise, these effects were specific for 1,2,4-oxadiazoles, but not other toxic compounds.

Drug-resistant Ole1 mutations reduced 1,2,4-oxadiazole-induced growth inhibition in wild-type cells (Fig. 3A). The same mutations also increased the EC50 (concentration that gives half-maximal response) in the context of the alpha-synuclein model, which is consistent with reduced binding to the

target. These shifts in dose response were specific for 1,2,4-oxadiazoles. These data further support that Ole1/SCD is the target for both growth inhibition and rescue of toxicity in disease models.

The *OLE1* gene is essential in *Saccharomyces cerevisiae*. However, strains deleted for *OLE1* (*ole1Δ*) are viable if their growth media is supplemented with oleic/palmitoleic acid. The *ole1Δ* strain supplemented with exogenous fatty acids was fully resistant to 1,2,4-oxadiazoles (Fig. 4). In other words, in the absence of the target, Ole1, the 1,2,4-oxadiazoles do not have growth inhibition activity. Independently, a chemical genetics approach identified *MGA2*, the transcription factor that regulates Ole1. Genetic deletion of *MGA2* (*mga2Δ*) phenocopied the effects of 1,2,4-oxadiazoles (Fig. 5). *mga2Δ* cells have reduced Ole1 levels, which itself rescues toxicity in the yeast disease models (e.g., the ApoE4 model). Supplementation of the growth media with oleic acid reversed this effect, similar to the results described above. Consistent with these data, treatment of yeast cells with the 1,2,4-oxadiazole Compound 2 inhibited lipid desaturation (Figs. 8A-8D). Overall, these data provide still further evidence that Ole1/SCD is the target of 1,2,4-oxadiazoles.

Humanized yeast strains expressing the human SCD proteins SCD1 or SCD5 were generated by genetic deletion of *OLE1* and expressing human SCD1 or SCD5 on a plasmid. Yeast expressing *OLE1* were resistant to known SCD1/SCD5 inhibitors such as A939572, CAY10566, MF-438, and MK-8245 (Fig. 6), suggesting that they do not target the yeast enzyme. In marked contrast, in the SCD1 and SCD5 humanized strains, the known SCD1/SCD5 inhibitors were extremely potent, with low nanomolar half-maximal inhibitory concentration (IC50) values (Fig. 6).

The effect of 1,2,4-oxadiazoles was also evaluated in both of the humanized SCD1 and SCD5 models. 1,2,4-oxadiazoles inhibited the growth of the SCD1 and/or SCD5 yeast strains, and differences in the structure-activity relationship (SAR) between the three SCD proteins was observed (Fig. 7). Some compounds inhibited the growth of both the SCD1 and the SCD5 strains. Other compounds appeared to target only the yeast enzyme. Out of a total of 250 1,2,4-oxadiazoles tested, 117 compounds exhibited significant activity (e.g., greater than 50% inhibition of growth) against the human enzymes, i.e., SCD1 and/or SCD5. The divergent SAR provides additional strong evidence for SCD being the target of 1,2,4-oxadiazoles.

Finally, treatment of yeast cells with the 1,2,4-oxadiazole Compound 2 inhibited lipid desaturation (Figs. 8A-8D), providing additional confirmatory evidence that SCD is the target of 1,2,4-oxadiazoles.

Taken together, these data demonstrate that Ole1/SCD is the target of 1,2,4-oxadiazoles, and that these compounds inhibit Ole1/SCD. Further, these data show that inhibition of Ole1/SCD rescues cell toxicity associated with expression of neurological disease proteins in yeast models, including ApoE4 and alpha-synuclein models, suggesting that SCD inhibition as a therapeutic approach for neurological disorders including Alzheimer's disease and Parkinson's disease.

Example 2: SCD Inhibition Rescues Alpha-Synuclein-Dependent Cell Toxicity, Neurite Degeneration, and Neuronal Cell Death

A. Materials and Methods

Molecular Biology and Compound Sources

Expression constructs for alpha-synuclein wild-type and A53T (SNCA), empty vector controls (pcDNA, pCAGGs), and mRab1a were obtained from the Whitehead Institute (Massachusetts Institute of

Technology, Cambridge, MA). The pSF-CAG plasmid was obtained from Oxford Genetics (Oxford, UK). The red fluorescent protein (RFP) reporter plasmid, pSF-MAP2-mApple, was constructed by replacing the CAG promoter with human MAP2 promoter sequence, and inserting mApple coding sequence into the multiple cloning site. The RFP reporter plasmid, pSF-CAG-mKate2, was generated by inserting the mKate2 coding sequence into pSF-CAG plasmid by PCR assembly. CAY10566 was purchased from Abcam. "SMARTpool" siRNAs for SCD1 and SCD5 were purchased from GE Dharmacon.

Cell Culture

U2OS cells (Sigma-Aldrich) between passages 12 to 22 were cultured in McCoy's 5A medium (ATCC) supplemented with 10% heat inactivated fetal bovine serum (Thermo Fisher). Induced pluripotent stem cells (iPSC)-derived neurons containing a triplication in the SCNA gene (S3) were maintained in brain-derived neurotrophic factor (BDNF), cyclic adenosine monophosphate (cAMP), and glial cell-line derived neurotrophic factor (GDNF)-supplemented growth medium as previously described (Chung et al. *Science* 342(6161):983-987, 2013). Four weeks after cells were differentiated into neurons, cells were harvested and RNA was extracted. PC12 cells (ATCC) were cultured in F12K medium supplemented with 15% horse serum and 2.5 % fetal bovine serum (Thermo Fisher). RNA extracted from the rat PC12 cells (passage 22) was used as a negative control for the expression of SCD1 and SCD5.

RNA Purification and Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

Cells (iPSC-derived neurons, PC12 and U2OS) were rinsed with ice-cold PBS (pH 7.4). Total RNA was purified using an RNEasy® Mini Kit following the manufacturer's instructions (Qiagen). Reverse transcription was performed with 150 ng RNA using a High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher) in a MASTERCYCLER® Pro thermal cycler (Eppendorf). Real-time PCR analyses of 2 µL cDNA products in a total reaction volume of 20 µL were carried out in duplicates using TaqMan® Fast Advanced Master Mix in a StepOnePlus™ Real-Time PCR System (Thermo Fisher). The primer pairs and probes for real-time amplification of SCD1 and SCD5 were predesigned TaqMan® gene expression assays (Applied Biosystems # Hs01682761_m1 and #Hs00227692_m1, respectively). Human beta-actin was used as an endogenous housekeeping control (Applied Biosystems #4310881E). The relative quantity of gene transcript abundance was calculated using the $\Delta\Delta C_t$ method.

Western Immunoblotting

Cells were rinsed with ice-cold PBS and lysed in ice-cold radioimmunoassay precipitation buffer (RIPA, Thermo Fisher) containing protease and phosphatase inhibitor cocktails (Sigma-Aldrich) for 15 min on ice. The lysates were centrifuged at 10,000 x g for 10 min at 4°C. Supernatant was collected and protein concentrations were measured using a bicinchoninic acid (BCA) kit (Pierce). Ten micrograms of total protein were resolved in 4-12% NuPAGE® Bis-Tris gels (Thermo Fisher) by electrophoresis then transferred to nitrocellulose membranes using the iBlot® system (Thermo Fisher). Membranes were blocked in 1:1 dilution of ODYSSEY® blocking buffer (LI-COR Biosciences) and PBS for 1 h at room temperature followed by incubation with primary anti-SCD1 (1/1000 dilution, Abcam) and anti-β-tubulin (1/4000 dilution, Sigma-Aldrich) antibodies in blocking buffer containing 0.1% of TWEEN®-20 at 4°C overnight with gentle rocking. After three washes with PBS plus 0.1% TWEEN®-20 (PBST), blots were

incubated with secondary antibodies conjugated to IRDye® 680 or 800 (1:8,000, Rockland Immunochemicals) in blocking buffer for 2 hours at room temperature. After three washes with PBST and two with water, blots were scanned in an ODYSSEY® quantitative fluorescent imaging system (LI-COR Biosciences).

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U2OS Cell Transfection

U2OS cells were trypsinized using 0.25% trypsin-EDTA (Thermo Fisher) for 5 min at 37°C followed by centrifugation at 800 rpm for 5 min at room temperature. Cell pellets were re-suspended in SE solution (Lonza Biologics, Inc.) at a density of 1×10^4 cells/ μ L. Alpha-synuclein wild-type or empty control (pcDNA) plasmids were transfected at a ratio of 10 mg per 1,000,000 cells. For genetic modifier studies, mRab1a was titrated at various concentrations in the presence of SNCA plasmids. Nucleofection was performed using 4D-NUCLEOFECTOR™ System (Lonza Biosciences, Inc.) under program code CM130 in either 20 μ L Nucleocuvette™ strips or 100 μ L single Nucleocuvettes™. Cells recovered at room temperature for 10-15 minutes after nucleofection before further handling. Pre-warmed medium was added and cells were thoroughly but gently mixed to a homogenous suspension before plating. Cells were seeded at 2×10^4 cells/100 μ L/well into 96 well PLD-coated white plates (Corning, Inc.) using a customized semi-automated pipetting program (VIAFLO 384/96, Integra Biosciences).

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U2OS ATP Assay

Powders of reference SCD inhibitors (CAY10566, A939572 and MF-438) were resuspended and serially diluted in DMSO. Compound treatment solutions were then prepared in complete U2OS growth medium such that compounds were held at 6-fold higher than the final intended treatment concentration. At 4 h after nucleofection, 20 μ L of the 6x compound solutions were then added to wells containing SNCA transfected cells and 100 μ L growth media. The final DMSO concentration was 0.3%. Plates were gently rocked to mix the drug solution into well media, and plates were incubated for 72 h with the compounds. Plates were sealed with MicroClima® lids (Labcyte Inc.) to reduce evaporation and variability. ATP content was then measured using the CellTiter-Glo® kit (Promega) with luminescence signals measured on an EnVision multimode plate reader (Perkin Elmer).

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Primary Neuron Transfections

Rat primary cortical neurons cultured in 96-well plates (Greiner Bio-One) were co-transfected with a fluorescence reporter plasmid (encoding mKate2) and empty or alpha-synuclein-A53T overexpression plasmids by lipofection at 5-6 div (days *in vitro*). LIPOFECTAMINE® 2000 transfection reagent (Thermo Fisher) (0.5µl/well) was diluted in NEUROBASAL® media (Thermo Fisher) and incubated for 5-10 min. The LIPOFECTAMINE®/NEUROBASAL® mixture was then added dropwise to a plasmid cocktail diluted in NEUROBASAL® media, and incubated for approximately 40 min. During this time, conditioned media on the neurons was replaced with media containing 1x kynurenic Acid (Sigma-Aldrich) in NEUROBASAL® media (NBKY). LIPOFECTAMINE®/DNA complex solutions were subsequently added dropwise to neurons in the NBKY media in the 96-well plate. Lipofection was carried out for 30-40 min in a standard cell culture incubator (37°C, 5% CO₂). Neurons were then washed with NEUROBASAL® media, and 50% conditioned/50% fresh NEUROBASAL® media containing B-27 supplement and GlutaMax™ (Thermo Fisher) (NBM) was applied to the cultures.

Human control and patient-derived trans-differentiated neurons were transfected with an RFP reporter driven by the human MAP2 promoter (MAP2-mApple) following the protocol for rat primary neurons as described above with the following exceptions: lipofection was carried out for approximately 1 h, and the final media replacement was with BrainPhys™ media supplemented with BDNF, GDNF, cAMP, ascorbic acid, and laminin.

Neurite Degeneration Assay

Transfected rat cortical neuron cultures were treated with DMSO or CAY10566 compound 4-6 h post-transfection. Vehicle or compound were diluted in NBM at the indicated concentrations. Culture plates were imaged at 6 h intervals in the IncuCyte® ZOOM (Essen Bioscience) incubator/imaging system for approximately 1 week. Neurite lengths of transfected neurons were tracked by an RFP reporter, mKate2, and measured by NeuroTrack™ Software Module (Essen Bioscience). Neurite lengths were normalized to the peak neurite length for each transfection group (6 replicate wells) and plotted to assess the neurite degeneration phase.

Neuron Survival Assay

Transfected neuronal cultures were imaged at 12-24 h intervals for the indicated number of days by robotic microscopy. Fluorescence images were acquired with a Nikon Eclipse Ti microscope equipped with a motorized stage, 20x extra-long working distance (ELWD) objective, and an Andor Zyla CMOS camera. During image acquisition, microplates were enclosed in an on-stage environmental chamber controlling temperature, CO₂, and humidity (Okolab). Images were processed and analyzed with custom-made scripts in R and ImageJ software. The lifetimes of individual neurons were determined by tracking fluorescently-labeled neurons in ImageJ. Neuronal death was determined to occur upon incidence of RFP signal loss or rupture of cell body. Cox proportional hazards analysis was used to generate cumulative hazard plots and determine the risk of neuron death. Log-rank test was used to determine statistical significance of survival curve divergence between neuron cohorts.

B. Results

To investigate the cellular events related to alpha-synuclein pathology, an assay was developed to measure the effects of alpha-synuclein expression on cellular ATP content in transfected U2OS cells, which is a general proxy for cell health and viability. U2OS cells transfected with alpha-synuclein exhibited a significant reduction in cellular ATP levels relative to cells transfected with the "empty" pCDNA vector control (Fig. 10). To evaluate the relevance of this alpha-synuclein-dependent decrease in ATP levels, U2OS were co-transfected with alpha-synuclein and mammalian Rab1a (mRab1a, a Rab GTPase family member), which is a known genetic modifier of alpha-synuclein toxicity in neurons and is involved in intracellular vesicle trafficking (Cooper et al. *Science* 313(5785):324-328, 2006). Co-transfecting mRab1a into U2OS cells with alpha-synuclein demonstrated that cellular ATP levels were significantly higher in co-transfected cells as compared to alpha-synuclein alone. This rescue of alpha-synuclein toxicity is reminiscent of that which occurs in neurons, indicating that the alpha-synuclein-dependent decrease of ATP content in U2OS cells may be recapitulating similar cellular pathological events. This indicates the U2OS model is useful for evaluating alpha-synuclein biology and toxicity.

Humans are known to express two different isoforms of stearoyl-CoA desaturase, SCD1 and SCD5 (Wang et al., *Biochem. Biophys. Res. Commun.* 332(3):735-42, 2005). SCD1 and SCD5 transcript levels were first evaluated by RT-PCR to determine whether the human U2OS cell line could be used to characterize the effects of SCD inhibitors. Analysis of mRNA isolated from U2OS cells demonstrated that this cell line expressed measurable levels of both SCD1 and SCD5, with approximately 4-fold higher relative levels of SCD1 (Fig. 11A). As a positive control for the SCD1 and SCD5 RT-PCR probe sets, RNA extracted from human iPSC-derived neurons containing a triplication of the alpha-synuclein gene (S3 neurons) was also analyzed, as human brain samples have previously been shown to express both SCD1 and SCD5 (Wang et al., *supra*). Similar to published results, cultures of human S3 neurons were found to express both SCD1 and SCD5, with approximately 25% higher expression of SCD1. RNA extracts prepared from rat PC12 cells demonstrated the specificity of the human probe sets, as no significant amplification was detected in these samples.

To confirm and extend the RT-PCR results, cell extracts from S3 neurons and U2OS cells were analyzed for expression of SCD1 protein by Western immunoblotting. This analysis confirmed that both cell populations expressed SCD1 at similar levels, relative to a beta-tubulin loading control (Fig. 11B). Attempts to measure SCD5 protein in these cell preparations were unsuccessful, as the commercially available antibody appeared unsuitable for this purpose.

The potential role of SCD in mediating alpha-synuclein-induced toxicity in U2OS cells was evaluated by siRNA knockdown of SCD1 and SCD5 expression. U2OS cells were transfected with empty vector controls, or the same plasmid containing alpha-synuclein. Cells were also co-treated with either a control scrambled siRNA, or siRNAs against human SCD1 or SCD5. Cells treated with SCD1 siRNA exhibited a general increase in ATP levels in either the presence or absence of alpha-synuclein. Thus, a specific role of SCD1 in mediating alpha-synuclein toxicity could not be evaluated under these experimental conditions. However, SCD5 knockdown resulted in a concentration-dependent rescue, which inversely correlated with levels of SCD5 mRNA (Figs. 12A and 12B), suggesting that decreasing SCD5 transcript, and subsequently protein and activity, provided a beneficial effect.

To further investigate a potential role of SCD in mediating alpha-synuclein cell toxicity, U2OS cells transfected with alpha-synuclein were also treated with a titration of a commercially available SCD inhibitor (CAY10566). ATP levels were assessed 72 h after treatment. CAY10566 significantly reversed alpha-synuclein-dependent decreases in ATP levels in a concentration-dependent fashion (Fig. 13).

These data indicate that inhibiting SCD activity in U2OS cells ameliorated the pathological effects of alpha-synuclein on overall cellular health.

The role of SCD in mediating alpha-synuclein-dependent pathological process was next investigated in a more relevant neuronal system. Primary cultures of rat cortical neurons were transfected with α -synuclein containing the A53T mutation and also treated with a titration of CAY10566.

Neurite length was measured in live cells every 6 hours after transfection for a total of 7 days.

Transfected cells were tracked with a fluorescent reporter (mCherry). Relative to DMSO controls, cells transfected with α -synuclein and treated with CAY10566 exhibited a concentration-dependent decrease in neurite degeneration (Fig. 14). Cells treated with the highest concentrations of CAY10566 (10 nM and 3 nM) exhibited slower neurite degeneration that was overlapping with control cultures that were not transfected with alpha-synuclein A53T, suggesting a complete rescue of alpha-synuclein detrimental effects. These data indicate that inhibition of SCD activity with CAY10566 was sufficient to reduce the pathological effects of alpha-synuclein overexpression on neurite degeneration.

To evaluate the effects of SCD inhibition in human neurons, human iPSC cells harboring the alpha-synuclein A53T mutation or an isogenic control line in which the A53T mutation was corrected to wild-type, were trans-differentiated into neurons, and cell survival was monitored over the course of 8 to 10 d. Analysis of cumulative single cell survival data indicated that the risk of neuron death was significantly reduced by treatment with CAY10566 at 100 nM and 30 nM (Fig. 15) relative to DMSO controls in the A53T neurons. Interestingly, at these concentrations of CAY10566, the risk of cell death was reduced back to levels observed in the isogenic control neurons, suggesting the enhanced toxicity of alpha-synuclein A53T on cell viability was eliminated.

Taken together, these data demonstrate that SCD1 and/or SCD5 inhibition rescues a number of phenotypes associated with neurological diseases in relevant disease models, providing further evidence that SCD inhibition as a therapeutic approach for neurological diseases including Alzheimer's disease and Parkinson's disease.

Example 3: Selective Inhibition of SCD5, as Well as Inhibition of SCD1 and SCD5, Reduce Risk of Neuron Death from α -Synuclein Toxicity and Result in Pharmacodynamic Responses in the Brain

A model of α -synuclein toxicity utilizing transient transfection into human iPSC-derived neurons was developed. In response to α -synuclein transfection, human neurons exhibit a significantly increased risk of death that can be tracked in live cells over the course of several days. This model was utilized to evaluate the role of SCD in α -synuclein-dependent neuronal toxicity. Human iPSC-derived neurons were transfected with a construct encoding A53T α -synuclein or an empty vector control. A53T α -synuclein-transfected cells were subsequently treated with a titration of the reference non-selective SCD inhibitor CAY10566 or DMSO as a vehicle control. Analysis of cumulative single cell survival data indicated that relative to DMSO controls, the risk of neuron death was significantly reduced by treatment with CAY10566 at all tested concentrations in the A53T α -synuclein neurons (Fig. 16 and Table 1). Within the

relatively narrow 10-fold concentration range tested (3 μ M to 0.3 μ M), there was no indication of a concentration-dependent effect. This may indicate a saturation of the maximal protective effect at the tested concentrations, or that higher doses are overall less well tolerated by the cells, so any enhanced protection could be obscured by general toxicity.

5 To better understand the relative contributions of different SCD isoforms in promoting protection against A53T α -synuclein toxicity, tool compounds were developed that exhibited an SCD5-selective inhibitor profile. Compounds with this selectivity profile have not been previously described in the literature. SCD5 Selective Inhibitor 1 (SCD5-SI-1) is a SCD5-selective compound that exhibits sub-micromolar potency in yeast growth inhibition assays, and was selected for further study in mammalian
10 cells. Human iPSC-derived neurons were transfected with a construct encoding A53T α -synuclein or an empty vector control. A53T α -synuclein transfected cells were subsequently treated with a titration of the SCD5-selective inhibitor SCD5 Selective Inhibitor 1 or DMSO as a vehicle control. Analysis of cumulative single cell survival data indicated that relative to DMSO controls, the risk of neuron death was significantly reduced by treatment with SCD5 Selective Inhibitor 1 at all tested concentrations in the A53T α -synuclein
15 neurons (Fig. 17). Within the relatively narrow 10-fold concentration range tested (5 μ M to 0.6 μ M), there was no indication of a concentration-dependent effect. This may indicate a saturation of the maximal protective effect at the tested concentrations, or that higher doses are overall less well tolerated by the cells, so any enhanced protection could be obscured by general toxicity.

To identify potential central nervous system (CNS) pharmacodynamic markers that respond to
20 inhibition of SCD, guinea pigs were selected as a model organism. Unlike rats and mice, guinea pigs express an SCD isoform similar to human SCD5, and expression of this isoform is enriched in the brain. For these reasons, this species was selected for evaluating both SCD5-selective and non-selective inhibitors. Potential effects of SCD inhibitors on steady state brain fatty acid saturation state, as well as all fatty acid levels, were evaluated by dosing guinea pigs orally twice a day for 5 days with either vehicle,
25 SCD5-selective compounds (SCD5 Selective Inhibitor 1 or SCD5 Selective Inhibitor 2), or non-selective SCD inhibitors (CAY10566 or SCD1/SCD5 Inhibitor 1 ("SCD1/5-1")). SCD5 Selective Inhibitor 1 is a SCD5-selective compound with >3000-fold selectivity over SCD1 that exhibits sub-micromolar potency in yeast growth inhibition assays. SCD5 Selective Inhibitor 2 is a SCD5-selective compound with >500-fold selectivity over SCD1 that exhibits sub-micromolar potency in yeast growth inhibition assays.
30 SCD1/SCD5 Inhibitor 1 approximately equivalent potency towards SCD1 and SCD5 that exhibits sub-micromolar potency in yeast growth inhibition assays. All compounds were evaluated at 25 mg/kg. On the last day of the study, the brains from these guinea pigs were harvested and evaluated for changes in fatty acid levels and saturation status. The desaturation index (DI) was calculated for 16 and 18 carbon chain fatty acids (C16 and C18 respectively) by taking the ratio of desaturated to saturated fatty acid of
35 each species. Relative to vehicle, all compounds significantly reduced the C16 DI (Fig. 18A). No significant effects were observed on the C18 DI (Fig. 18B). The relative levels of individual monounsaturated C16 fatty acids (expressed as the % composition of total) was also evaluated. For both positional isomers of monounsaturated C16 fatty acids, C16:1n7 and C16:1n9, inhibitors of both SCD1/SCD5 selectivity profiles significantly reduced monounsaturated fatty acid levels (Figs. 18C and
40 18D). The data in Figs. 18A-18D are consistent with compounds having SCD inhibitory activity, in which there is a decrease in the levels of unsaturated fatty acids. The C16:1n9 fatty acid is derived from

C18:1n9 through beta-oxidation. Thus, a decrease in this fatty acid indicated that although no effects were observed in the overall C18 DI, there was a reduction in the monounsaturated C18 species. Interestingly, probing brain samples for the relative levels of linoleic acid (18:2n6) (Fig. 18E) and gamma-linoleic acid (18:3n6) (Fig. 18F) revealed that levels of these essential omega-6 fatty acids both
5 significantly increased with administration of SCD5-selective or non-selective compounds. This inverse relationship in changes to mono- and poly-unsaturated fatty acid levels is consistent with reports in the literature. These data all indicate that both selective inhibition of SCD5, as well as inhibition of both SCD isoforms, result in a measurable pharmacodynamic response in the tissue of interest for CNS indications.

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Other Embodiments

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent
15 arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition
20 provided herein is to serve as the definition for the term.

Other embodiments are in the claims.

CLAIMS

What is claimed is:

- 5 1. Use of an SCD5 inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is Parkinson's disease or dementia with Lewy bodies.
2. The use of claim 1, wherein the subject has an elevated level, or is predicted to have an
10 elevated level of α -synuclein, ApoE4, or an undesired form thereof.
3. The use of claim 1 or 2, wherein the SCD5 inhibitor further inhibits SCD1.
4. The use of claim 1 or 2, wherein the SCD5 inhibitor is selective for SCD5 over SCD1.
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5. The use of claim 1 or 2, wherein the subject carries one or two copies of the ApoE4 allele.
6. The use of any one of claims 1 to 5, wherein the neurological disorder is Parkinson's
 disease.
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7. The use of any one of claims 1 to 5, wherein the neurological disorder is Lewy body
 dementia.
8. The use of any one of claims 1 to 7, wherein an additional therapeutic agent is to be
25 administered to the subject.
9. The use of claim 8, wherein the additional therapeutic agent is a small molecule, an antibody
 or fragment thereof, or a nucleic acid.
- 30 10. The use of claim 8 or 9, wherein the additional therapeutic agent is a cognition-enhancing
 agent, an antidepressant agent, an anxiolytic agent, an antipsychotic agent, a sedative, a dopamine
 promoter, or an anti-tremor agent.
11. The use of claim 1, wherein the SCD5 inhibitor is to be administered in an amount sufficient
35 to suppress toxicity in a cell related to protein misfolding and/or aggregation.