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 embodiments, the disease or disorder is a neurological disorders.

In one aspect, the disclosure provides use of an SCD inhibitor in an amount sufficient to suppress toxicity in a cell related to protein misfolding and/or aggregation, in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof.

In another aspect, the disclosure provides use of an SCD inhibitor in the manufacture of a medicament for suppressing toxicity in a cell related to protein misfolding and/or aggregation in a subject.

In another aspect, the disclosure provides use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein:

(a) the expression level of α-synuclein, ApoE4, or an undesired form thereof is to be determined in the subject; and

(b) an effective amount of the medicament is to be administered to the subject if the level of α-synuclein , ApoE4, and/or the undesired form thereof is greater than a predetermined level.

In another aspect, the disclosure provides use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disease in a subject in need thereof, wherein the subject has an elevated level, or is predicted to have an elevated level of α-synuclein, ApoE4, or an undesired form thereof.

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.

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, 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^{10} is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl or C_1-C_{12}alkoxy; 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(R^4)-, -O-, -S(O)$_t$ (where t is 0, 1 or 2), -C(R^4)= or -C(R^4)=C(R^4)-;

J and K are each independently N or C(R^{10});

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

V is direct bond, -N(R^1)-, -N(R^1)C(O)-, -O-, -C(O)-, -C(O)O-, -C(S)-, -C(O)N(R^1)-, -S(O)$_p$- (where p is 1 or 2), or -S(O)$_p$N(R^1)- (where p 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_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^{10} is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl or C_1-C_{12}alkoxy; 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, the disclosure provides compounds of Formula Ib having the following Formula Iba:

each R^{13} is independently selected from hydrogen or C_1-C_6alkyl; 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(R^1)-, -C(R^1)$_2$-, -C(O)-, -OC(O)-, -S(O)$_t$- (where t is 0, 1 or 2), -N(R^1)S(O)$_t$- (where t is 1 or 2), -S(O)$_2$N(R^1)-, -C(O)N(R^1)-, -C(S)N(R^1)-, -OS(O)$_2$N(R^1)-, -OC(O)N(R^1)-, -OC(S)N(R^1)-, -N(R^1)C(O)N(R^1)- or -N(R^1)C(S)N(R^1)-;

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

R^4, R^5, and R^6 are each independently selected from hydrogen, bromo, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro, or -N(R^{13})$_2$;

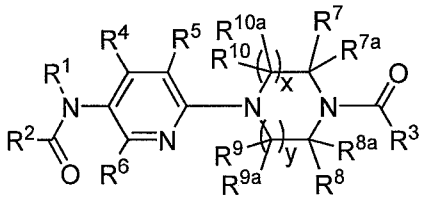
In some embodiments of the compound of Formula IVb,

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

V is -C(O)-, -C(S)-, -C(O)N(R^1)-, -C(O)O-, -S(O)$_2$-, -S(O)$_2$N(R^1)- or -C(R^{11})H-;

R^4, R^5, and R^6 are each independently selected from hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, cyano, nitro, or -N(R^{13})$_2$;

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



(IVca)

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_1-C_{12}heteroaryl, C_3-C_{12}heterocyclylalkyl, C_3-C_{12}heterocyclyl, and C_3-C_{12}heteroarylalkyl, provided that R^2 is not pyrazinyl, pyridinonyl, pyrrolidinonyl or imidazolyl;

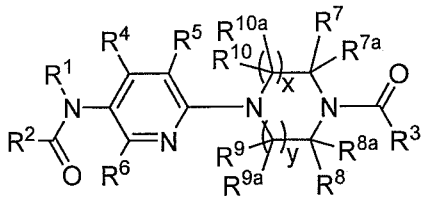
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

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_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;

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_3alkyl;

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



(IVcb)

wherein:

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_6alkoxy, 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;

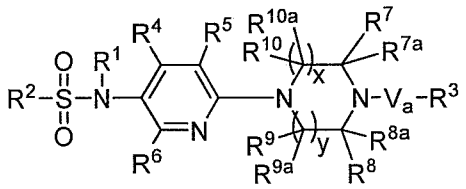
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C_1-C_6alkyl, C_1-C_6trihaloalkyl, C_1-C_6trihaloalkoxy, C_1-C_6alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

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_3alkyl; and

each R^{12} is independently selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, aryl or aralkyl.

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



(IVd)

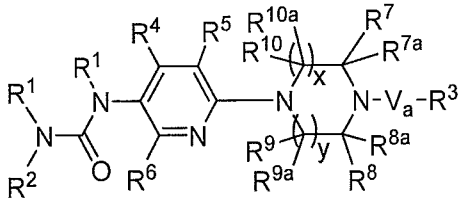
wherein:

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);

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_6alkoxy, 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.

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



(IVe)

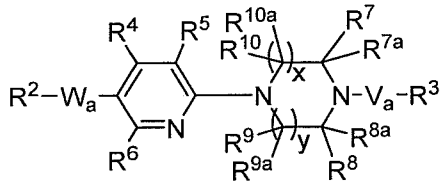
wherein:

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)$_t$N(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, 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 Formula IVf:



(IVf)

wherein:

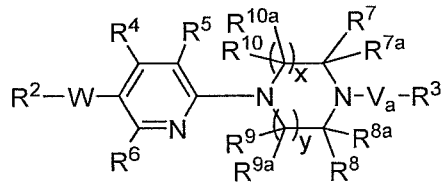
W_a is -O-, -N(R^1)-, -S(O)$_t$- (where t is 0, 1 or 2);

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)$_t$N(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, 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 Formula IVaa:



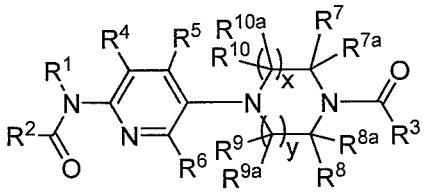
(IVaa)

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 $-C(R^{11})H$.

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



(IVha)

wherein:

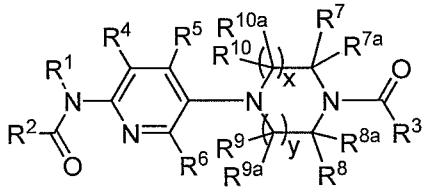
R^2 is selected from the group consisting of C_7-C_{12}alkyl, C_3-C_{12}alkenyl, C_7-C_{12}hydroxyalkyl, C_1-C_{12}alkoxy, C_2-C_{12}alkoxyalkyl, C_3-C_{12}hydroxyalkenyl, C_3-C_{12}cycloalkyl, C_4-C_{12}cycloalkylalkyl, C_{13}-C_{19}aralkyl, C_1-C_{12}heteroaryl, C_3-C_{12}heterocyclylalkyl and C_3-C_{12}heteroarylalkyl,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

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_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_3alkyl.

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



(IVhb)

wherein:

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_6alkoxy, 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;

or R^2 is phenyl optionally substituted with one or more substituents selected from halo and C_1-C_6trihaloalkyl;

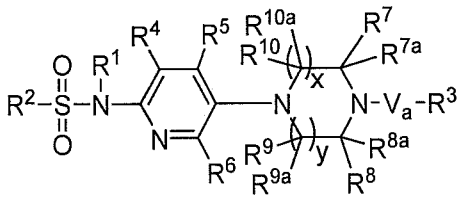
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

R^3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxyl, C_1-C_6alkyl, C_1-C_6trihaloalkyl, C_1-C_6trihaloalkoxy, C_1-C_6alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

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_3alkyl;

each R^{12} is independently selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, aryl or aralkyl.

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



(IVi)

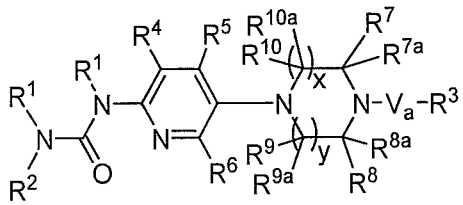
wherein:

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

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_6alkoxy, 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.

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



(IVj)

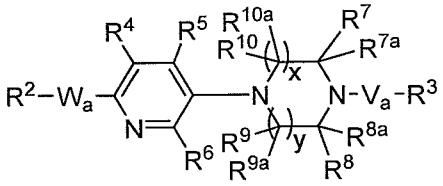
wherein:

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

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.

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



(IVk)

wherein:

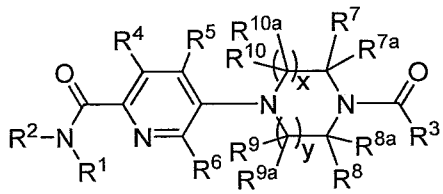
W_a is -O-, -N(R^1)- or -S(O)$_t$- (where t is 0, 1 or 2);

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

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:



(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}heterocyclylalkyl, 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, 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;

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.

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

$-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$, $-N(R^1)C(O)O-$;

R^3 is selected from the group consisting of 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 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;

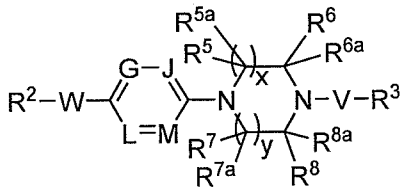
each R^4 is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, haloalkyl, cyano, nitro or $-N(R^9)_2$;

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 bridge 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_3alkyl;

R^{10} is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl or C_1-C_{12}alkoxy;

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



(Vc)

wherein:

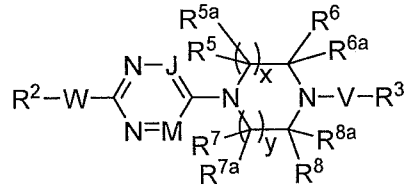
W is $-N(R^1)C(O)-$, $-C(O)N(R^1)-$, $-OC(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$, $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-N(R^1)S(O)_2-$, $-S(O)_2N(R^1)-$, $-C(O)-$, $-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$ or $-N(R^1)C(O)O-$;

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

G, J, L and M are each independently selected from $-N=$ or $-C(R^4)=$; provided that at least two of G, J, L and M are $-N=$, and provided that when G and J are both $-C(R^4)=$, L and M cannot both be $-N=$, and when L and M are both $-C(R^4)=$, 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.

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



(Vd)

wherein:

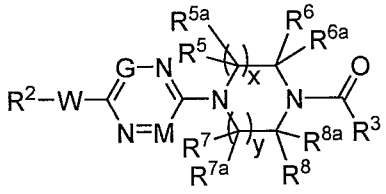
W is $-N(R^1)C(O)-$, $-C(O)N(R^1)-$, $-OC(O)N(R^1)-$, $-N(R^1)C(O)N(R^1)-$, $-O-$, $-N(R^1)-$, $-S(O)_t-$ (where t is 0, 1 or 2), $-N(R^1)S(O)_2-$, $-S(O)_2N(R^1)-$, $-C(O)-$, $-OS(O)_2N(R^1)-$, $-OC(O)-$, $-C(O)O-$ or $-N(R^1)C(O)O-$;

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 $-C(R^4)=$;

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:



(Ve)

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;

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_6alkyl, C_1-C_6trihaloalkyl, C_1-C_6trihaloalkoxy, C_1-C_6alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

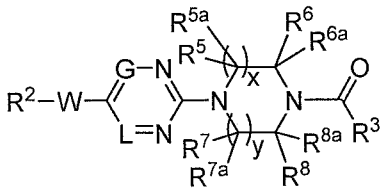
each R^5, R^{5a}, R^6, R^{6a}, R^7, R^{7a}, R^8 and R^{8a} is independently selected from hydrogen or C_1-C_3alkyl;

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_3alkyl;

each R^{12} is independently selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, 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 Vf:



(Vf)

wherein:

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

G and L 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;

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_6alkyl, C_1-C_6trihaloalkyl, C_1-C_6trihaloalkoxy, C_1-C_6alkylsulfonyl, $-N(R^{12})_2$, $-OC(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)_2N(R^{12})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

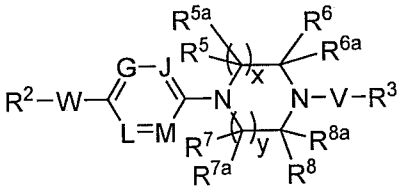
each R^5, R^{5a}, R^6, R^{6a}, R^7, R^{7a}, R^8 and R^{8a} is independently selected from hydrogen or C_1-C_3alkyl;

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_3alkyl;

each R^{12} is independently selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, 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:



(Vca)

wherein:

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

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

G, J, L and M are each independently selected from $-N=$ or $-C(R^4)=$; provided that at least two of G, J, L and M are $-N=$, and provided that when G and J are both $-C(R^4)=$, L and M cannot both be $-N=$, and when L and M are both $-C(R^4)=$, G and J cannot both be $-N=$;

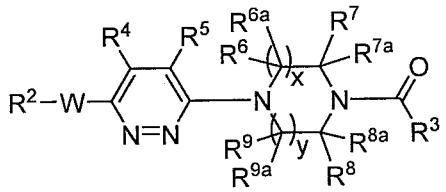
a stereoisomer, enantiomer or tautomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof or a prodrug thereof.

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.

each R^{12} is independently selected from hydrogen or C_1-C_6alkyl;

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 Formula VIa:



(VIa)

wherein:

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

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}heterocyclylalkyl, and C_3-C_{12}heteroarylalkyl;

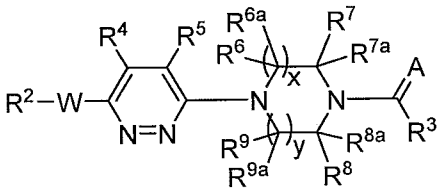
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, where some or all of the rings may be fused to each other;

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_{12}aralkyl, C_3-C_{12}heterocyclyl, C_3-C_{12}heterocyclylalkyl, 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, heterocyclyl, aryl and heteroaryl and where some or all of the 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:



(VIb)

wherein:

A is oxygen or sulfur;

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

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_6alkoxy, 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}heterocyclyl, C_3-C_{12}heterocyclylalkyl, C_1-C_{12}heteroaryl, and C_3-C_{12}heteroarylalkyl;

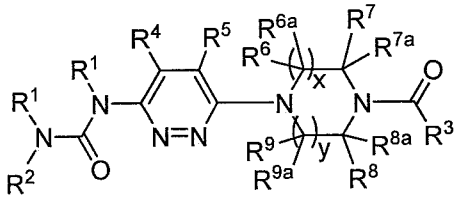
or R^2 is a multi-ring structure having 2 to 4 rings wherein the rings are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl and where some or all of the rings may be fused to each other;

R^3 is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C_1-C_6alkyl, C_1-C_6trihaloalkyl, C_1-C_6trihaloalkoxy, C_1-C_6alkylsulfonyl, $-N(R^{11})_2$, $-OC(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)_2N(R^{11})_2$, cycloalkyl, heterocyclyl, heteroaryl and heteroarylcycloalkyl, provided that R^3 is not phenyl substituted with optionally substituted thienyl;

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

each R^{11} is independently selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, aryl or aralkyl.

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



(VIc)

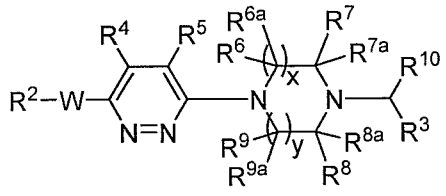
wherein:

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, C_3-C_{12}heterocyclyl, C_3-C_{12}heterocyclylalkyl, aryl, C_7-C_{19}aralkyl, 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^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 VIda:



(VIda)

wherein:

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

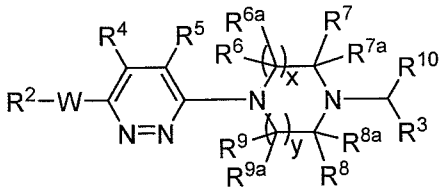
R^2 is selected from the group consisting of C_7-C_{12}alkyl, C_2-C_{12}alkenyl, C_7-C_{12}hydroxyalkyl, C_2-C_{12}hydroxyalkenyl, C_1-C_{12}alkoxy, C_2-C_{12}alkoxyalkyl, C_3-C_{12}cycloalkyl, C_4-C_{12}cycloalkylalkyl, C_{13}-C_{19}aralkyl, C_3-C_{12}heterocyclyl, C_3-C_{12}heterocyclylalkyl, C_1-C_{12}heteroaryl, and C_3-C_{12}heteroarylalkyl;

R^{10} is hydrogen or C_1-C_3alkyl; and

each R^{12} is independently selected from hydrogen or C_1-C_6alkyl;

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 VIdb:



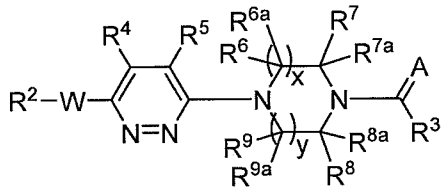
(VIdb)

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.

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



(VIb)

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)-, -OC(O)N(R^1)-, -N(R^1)S(O)$_p$- (where p is 1 or 2), -S(O)$_p$N(R^1)- (where p is 1 or 2), -C(O)-, -OS(O)$_2$N(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)$_p$N(R^1)- (where p is 1 or 2), -C(R^{10})H- or -C(=NR^{1a})-;

R^{1a} is selected from the group consisting of hydrogen, -OR^1, cyano, C_1-C_6alkyl 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 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:

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;

each R^4 is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, haloalkyl, cyano, nitro or -$N(R^9)_2$;

R^{10} is a hydrogen or C_1-C_3alkyl; and

R^{11} is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl or C_1-C_{12}alkoxy;

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 $C(R^{10})$;

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

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

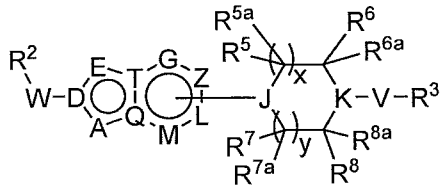
R^3 is selected from the group consisting of hydrogen, C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_{12}hydroxyalkyl, C_2-C_{12}hydroxyalkenyl, C_2-C_{12}alkoxyalkyl, C_3-C_{12}cycloalkyl, C_4-C_{12}cycloalkylalkyl, aryl, C_7-C_{19}aralkyl, C_3-C_{12}heterocyclyl, C_3-C_{12}heterocyclylalkyl, C_1-C_{12}heteroaryl and C_3-C_{12}heteroarylalkyl, provided that R^3 is not optionally substituted cyclopentyl or an optionally substituted 5-membered heterocyclic ring;

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^4 is hydrogen, fluoro, chloro, hydroxyl, C_1-C_{12}alkyl, C_1-C_{12}alkoxy, haloalkyl, cyano, nitro or -$N(R^9)_2$;

each R^{10} is independently selected from hydrogen, fluoro, chloro, C_1-C_{12}alkyl or C_1-C_{12}alkoxy.

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 $C(R^4)$;

T and Q are each independently C or N.

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

CLAIMS

What is claimed is:

1. Use of an SCD inhibitor in an amount sufficient to suppress toxicity in a cell related to protein misfolding and/or aggregation, in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof.

2. Use of an SCD inhibitor in the manufacture of a medicament for suppressing toxicity in a cell related to protein misfolding and/or aggregation in a subject.

3. The use of claim 1 or 2, wherein the toxicity in the cell is related to protein aggregation related to misfolding of a protein.

4. The use of any one of claims 1 to 3, wherein the toxicity in the cell is related to misfolding and/or aggregation of α-synuclein or ApoE4.

5. The use of any one of claims 1 to 4, wherein the cell is a neural cell.

6. The use of claim 5, wherein the neural cell is a neuron or glial cell.

7. Use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein:

(a) the expression level of α-synuclein, ApoE4, or an undesired form thereof is to be determined in the subject; and

(b) an effective amount of the medicament is to be administered to the subject if the level of α-synuclein , ApoE4, and/or the undesired form thereof is greater than a predetermined level.

8. Use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disease in a subject in need thereof, wherein the subject has an elevated level, or is predicted to have an elevated level of α-synuclein, ApoE4, or an undesired form thereof.

9. The use of claim 8, wherein the subject is predicted to have an elevated level of α-synuclein, ApoE4, and/or an undesired form thereof based on genetic markers.

10. The use of any one of claims 1 to 9, wherein the SCD inhibitor is an SCD1 inhibitor.

11. The use of claim 10, wherein the SCD1 inhibitor is selective for SCD1 over SCD5.

12. The use of anyone of claims 1 to 8, wherein the SCD inhibitor is an SCD5 inhibitor.

13. The use of claim 12, wherein the SCD5 inhibitor is selective for SCD5 over SCD1.

14. The use of any one of claims 1 to 13, wherein the subject carries one or two copies of the ApoE4 allele.

15. The use of any one of claims 1 to 14, wherein the SCD inhibitor is a compound of any one of Formula I-LXI, or any compound described herein.

16. The use of any one of claims 1 and 3 to 15, wherein the neurological disorder is Alzheimer's disease (AD), mild cognitive impairment (MCI), cerebral amyloid angiopathy (CAA), dementia associated with Down syndrome, or other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42.

17. The use of any one of claims 1 and 3 to 15, wherein the neurological disorder is AD, Parkinson's disease (PD), dementia with Lewy bodies, amyotrophic lateral sclerosis or Lou Gehrig's disease, Alpers' disease, Leigh's disease, Pelizaeus-Merzbacher disease, Olivopontocerebellar atrophy, Friedreich's ataxia, leukodystrophies, Rett syndrome, Ramsay Hunt syndrome type II, Down's syndrome, multiple sclerosis, and mild cognitive impairment (MCI).

18. The use of any one of claims 1 and 3 to 15, wherein the neurological disorder is a proteopathy.

19. The use of claim 18, wherein the proteopathy is a synucleinopathy.

20. The use of claim 19, wherein the synucleinopathy is 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.

21. The use of claim 18, wherein the proteopathy is AD, Alexander disease, amyotrophic lateral sclerosis (ALS), a prion disease, Huntington's disease, Machado-Joseph disease, Pick's disease, or frontotemporal dementia.

22. The use of claim 21, wherein the prion disease is Creutzfeldt-Jakob disease.

23. The use of any one of claims 1 and 3 to 15, wherein the neurological disorder is a neurodegenerative disorder.

24. The use of claim 23, wherein the neurodegenerative disorder is Alpers' disease, ataxia telangectsia, 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.

25. The use of any one of claims 1 and 3 to 15, wherein the neurological disorder is an ApoE-associated neurodegenerative disorder.

26. The use of claim 25, wherein the ApoE-associated neurodegenerative disorder is AD, vascular cognitive impairment, cerebral amyloid angiopathy, traumatic brain injury, or multiple sclerosis.

27. The use of claim 25 or 26, wherein the ApoE-associated disorder is AD.

28. The use of any one of claims 1 to 27, wherein an additional therapeutic agent is to be administered to the subject.

29. The use of claim 28, wherein the additional therapeutic agent is a small molecule, an antibody or fragment thereof, or a nucleic acid.

30. The use of claim 28 or 29, 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.