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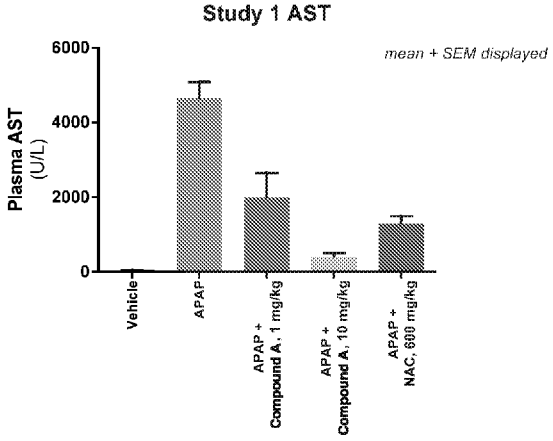
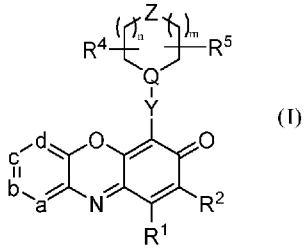


FIG. 1



(I)

(57) Abstract: Disclosed herein are compounds and methods of using such compounds for treating or suppressing oxidative stress disorders, including mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases and diseases of aging, or for treating or suppressing liver or kidney disorders characterized by one or more inflammation and/or oxidative stress biomarkers, or for modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, wherein the compounds are aryl- and heteroaryl-resorufin derivatives.

[Continued on next page]

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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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ARYL- AND HETEROARYL-RESORUFIN DERIVATIVES FOR TREATMENT OF OXIDATIVE STRESS DISORDERS AND LIVER AND KIDNEY DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application 62/443,641 filed on January 6, 2017, the contents of which are incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The application discloses compositions and methods useful for treatment or suppression of diseases, developmental delays, and symptoms related to oxidative stress disorders, and for treatment or suppression of liver and kidney disorders characterized by one or more inflammation and/or oxidative stress biomarkers, including liver disorders resulting from systemic inflammatory response syndrome (SIRS), sepsis, severe illness, traumatic injury to the liver, and exposure to liver toxins. Examples of oxidative stress disorders include mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases, and diseases of aging.

BACKGROUND

[0003] Oxidative stress is caused by disturbances to the normal redox state within cells. An imbalance between routine production and detoxification of reactive oxygen species such as peroxides and free radicals can result in oxidative damage to the cellular structure and machinery. The most important source of reactive oxygen species under normal conditions in aerobic organisms is probably the leakage of activated oxygen from mitochondria during normal oxidative respiration. Impairments associated with this process are suspected to contribute to mitochondrial disease, neurodegenerative disease, and diseases of aging.

[0004] Mitochondria are organelles in eukaryotic cells, popularly referred to as the "powerhouse" of the cell. One of their primary functions is oxidative phosphorylation. The molecule adenosine triphosphate (ATP) functions as an energy "currency" or energy carrier in the cell, and eukaryotic cells derive the majority of their ATP from biochemical processes carried out by mitochondria. These biochemical processes include the citric acid cycle (the tricarboxylic acid cycle, or Krebs cycle), which generates reduced nicotinamide adenine dinucleotide ($NADH + H^+$) from oxidized nicotinamide adenine dinucleotide (NAD^+), and oxidative phosphorylation, during which $NADH + H^+$ is oxidized back to NAD^+. (The citric

acid cycle also reduces flavin adenine dinucleotide, or FAD, to FADH2; FADH2 also participates in oxidative phosphorylation.)

[0005] The electrons released by oxidation of NADH + H^+ are shuttled down a series of protein complexes (Complex I, Complex II, Complex III, and Complex IV) known as the mitochondrial respiratory chain. These complexes are embedded in the inner membrane of the mitochondrion. Complex IV, at the end of the chain, transfers the electrons to oxygen, which is reduced to water. The energy released as these electrons traverse the complexes is used to generate a proton gradient across the inner membrane of the mitochondrion, which creates an electrochemical potential across the inner membrane. Another protein complex, Complex V (which is not directly associated with Complexes I, II, III and IV) uses the energy stored by the electrochemical gradient to convert ADP into ATP.

[0006] When cells in an organism are temporarily deprived of oxygen, anaerobic respiration is utilized until oxygen again becomes available or the cell dies. The pyruvate generated during glycolysis is converted to lactate during anaerobic respiration. The buildup of lactic acid is believed to be responsible for muscle fatigue during intense periods of activity, when oxygen cannot be supplied to the muscle cells. When oxygen again becomes available, the lactate is converted back into pyruvate for use in oxidative phosphorylation.

[0007] Oxygen poisoning or toxicity is caused by high concentrations of oxygen that may be damaging to the body and increase the formation of free-radicals and other structures such as nitric oxide, peroxynitrite, and trioxidane. Normally, the body has many defense systems against such damage but at higher concentrations of free oxygen, these systems are eventually overwhelmed with time, and the rate of damage to cell membranes exceeds the capacity of systems which control or repair it. Cell damage and cell death then result.

[0008] Qualitative and/or quantitative disruptions in the transport of oxygen to tissues result in energy disruption in the function of red cells and contribute to various diseases such as haemoglobinopathies. Haemoglobinopathy is a kind of genetic defect that results in abnormal structure of one of the globin chains of the hemoglobin molecule. Common haemoglobinopathies include thalassemia and sickle-cell disease. Thalassemia is an inherited autosomal recessive blood disease. In thalassemia, the genetic defect results in reduced rate of synthesis of one of the globin chains that make up hemoglobin. While thalassemia is a quantitative problem of too few globins synthesized, sickle-cell disease is a qualitative problem of synthesis of an incorrectly functioning globin. Sickle-cell disease is a blood

disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in their restricted movement through blood vessels, depriving downstream tissues of oxygen.

[0009] Mitochondrial dysfunction contributes to various disease states. Some mitochondrial diseases are due to mutations or deletions in the mitochondrial genome. If a threshold proportion of mitochondria in the cell is defective, and if a threshold proportion of such cells within a tissue have defective mitochondria, symptoms of tissue or organ dysfunction can result. Practically any tissue can be affected, and a large variety of symptoms may be present, depending on the extent to which different tissues are involved. In some embodiments, mitochondrial diseases are Friedreich's ataxia (FRDA), Leber's Hereditary Optic Neuropathy (LHON), mitochondrial myopathy, encephalopathy, lactacidosis, and stroke (MELAS), Myoclonus Epilepsy Associated with Ragged-Red Fibers (MERRF) syndrome, Leigh's Syndrome, Leigh-like Syndrome, and respiratory chain disorders. Most mitochondrial diseases involve children who manifest the signs and symptoms of accelerated aging, including neurodegenerative diseases, stroke, blindness, hearing impairment, vision impairment, diabetes, and heart failure.

[0010] Friedreich's ataxia is an autosomal recessive neurodegenerative and cardiodegenerative disorder caused by decreased levels of the protein Frataxin. The disease causes the progressive loss of voluntary motor coordination (ataxia) and cardiac complications. Symptoms typically begin in childhood, and the disease progressively worsens as the patient grows older; patients eventually become wheelchair-bound due to motor disabilities.

[0011] Leber's Hereditary Optic Neuropathy (LHON) is a disease characterized by blindness which occurs on average between 27 and 34 years of age. Other symptoms may also occur, such as cardiac abnormalities and neurological complications.

[0012] Mitochondrial myopathy, encephalopathy, lactacidosis, and stroke (MELAS) can manifest itself in infants, children, or young adults. Strokes, accompanied by vomiting and seizures, are one of the most serious symptoms; it is postulated that the metabolic impairment of mitochondria in certain areas of the brain is responsible for cell death and neurological lesions, rather than the impairment of blood flow as occurs in ischemic stroke.

[0013] Myoclonus Epilepsy Associated with Ragged-Red Fibers (MERRF) syndrome is one of a group of rare muscular disorders that are called mitochondrial encephalomyopathies.

Mitochondrial encephalomyopathies are disorders in which a defect in the genetic material arises from a part of the cell structure that releases energy (mitochondria). This can cause a dysfunction of the brain and muscles (encephalomyopathies). The mitochondrial defect as well as "ragged-red fibers" (an abnormality of tissue when viewed under a microscope) are always present. The most characteristic symptom of MERRF syndrome is myoclonic seizures that are usually sudden, brief, jerking spasms that can affect the limbs or the entire body. Difficulty speaking (dysarthria), optic atrophy, short stature, hearing loss, dementia, and involuntary jerking of the eyes (nystagmus) may also occur.

[0014] Leigh Disease or Leigh Syndrome is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system where the symptoms usually begin between the ages of 3 months to 2 years and progress rapidly. In most children, the first signs may be poor sucking ability and loss of head control and motor skills. These symptoms may be accompanied by loss of appetite, vomiting, irritability, continuous crying, and seizures. As the disorder progresses, symptoms may also include generalized weakness, lack of muscle tone, and episodes of lactic acidosis, which can lead to impairment of respiratory and kidney function. Heart problems may also occur.

[0015] Co-Enzyme Q10 Deficiency is a respiratory chain disorder, with syndromes such as (1) myopathy with exercise intolerance and recurrent myoglobin in the urine manifested by ataxia, seizures or mental retardation and leading to renal failure (Di Mauro et al., (2005) Neuromusc. Disord.,15:311-315); (2) childhood-onset cerebellar ataxia and cerebellar atrophy (Masumeci et al., (2001) Neurology 56:849-855 and Lamperti et al., (2003) 60:1206:1208); and (3) infantile encephalomyopathy associated with nephrosis. Biochemical measurement of muscle homogenates of patients with CoQ10 deficiency showed severely decreased activities of respiratory chain complexes I and II + III, while complex IV (COX) was moderately decreased (Gempel et al., (2007) Brain, 130(8):2037-2044).

[0016] Complex I Deficiency or NADH dehydrogenase NADH-CoQ reductase deficiency is a respiratory chain disorder, with symptoms classified by three major forms: (1) fatal infantile multisystem disorder, characterized by developmental delay, muscle weakness, heart disease, congenital lactic acidosis, and respiratory failure; (2) myopathy beginning in childhood or in adult life, manifesting as exercise intolerance or weakness; and (3) mitochondrial encephalomyopathy (including MELAS), which may begin in childhood or adult life and consists of variable combinations of symptoms and signs, including

ophthalmoplegia, seizures, dementia, ataxia, hearing loss, pigmentary retinopathy, sensory neuropathy, and uncontrollable movements.

[0017] Complex II Deficiency or Succinate dehydrogenase deficiency is a respiratory chain disorder with symptoms including encephalomyopathy and various manifestations, including failure to thrive, developmental delay, hypotonia, lethargy, respiratory failure, ataxia, myoclonus, and lactic acidosis.

[0018] Complex III Deficiency or Ubiquinoid-cytochrome C oxidoreductase deficiency is a respiratory chain disorder with symptoms categorized in four major forms: (1) fatal infantile encephalomyopathy, congenital lactic acidosis, hypotonia, dystrophic posturing, seizures, and coma; (2) encephalomyopathies of later onset (childhood to adult life) with various combinations of weakness, short stature, ataxia, dementia, hearing loss, sensory neuropathy, pigmentary retinopathy, and pyramidal signs; (3) myopathy, with exercise intolerance evolving into fixed weakness; and (4) infantile histiocytoid cardiomyopathy.

[0019] Complex IV Deficiency or Cytochrome C oxidase deficiency is a respiratory chain disorder with symptoms categorized in two major forms: (1) encephalomyopathy, where patients typically are normal for the first 6 to 12 months of life and then show developmental regression, ataxia, lactic acidosis, optic atrophy, ophthalmoplegia, nystagmus, dystonia, pyramidal signs, respiratory problems, and frequent seizures; and (2) myopathy with two main variants: (a) Fatal infantile myopathy-may begin soon after birth and accompanied by hypotonia, weakness, lactic acidosis, ragged-red fibers, respiratory failure, and kidney problems: and (b) Benign infantile myopathy- may begin soon after birth and accompanied by hypotonia, weakness, lactic acidosis, ragged-red fibers, respiratory problems, but (if the child survives) followed by spontaneous improvement.

[0020] Complex V Deficiency or ATP synthase deficiency is a respiratory chain disorder including symptoms such as slow, progressive myopathy.

[0021] CPEO or Chronic Progressive External Ophthalmoplegia Syndrome is a respiratory chain disorder including symptoms such as visual myopathy, retinitis pigmentosa, or dysfunction of the central nervous system.

[0022] Kearns-Sayre Syndrome (KSS) is a mitochondrial disease characterized by a triad of features including: (1) typical onset in persons younger than age 20 years; (2) chronic, progressive, external ophthalmoplegia; and (3) pigmentary degeneration of the retina. In addition, KSS may include cardiac conduction defects, cerebellar ataxia, and raised

cerebrospinal fluid (CSF) protein levels (e.g., >100 mg/dL). Additional features associated with KSS may include myopathy, dystonia, endocrine abnormalities (*e.g.*, diabetes, growth retardation or short stature, and hypoparathyroidism), bilateral sensorineural deafness, dementia, cataracts, and proximal renal tubular acidosis.

[0023] Maternally inherited diabetes and deafness (MIDD) is a mitochondrial disorder characterized by maternally transmitted diabetes and sensorineural deafness. In most cases, MIDD is caused by a point mutation in the mitochondrial gene MT-TL1, encoding the mitochondrial tRNA for leucine, and in rare cases in MT-TE and MT-TK genes, encoding the mitochondrial tRNAs for glutamic acid and lysine, respectively.

[0024] In addition to congenital disorders involving inherited defective mitochondria, acquired mitochondrial dysfunction contributes to diseases, particularly neurodegenerative disorders associated with aging like Parkinson's, Alzheimer's, and Huntington's Diseases. The incidence of somatic mutations in mitochondrial DNA rises exponentially with age; and diminished respiratory chain activity is found universally in aging people. Mitochondrial dysfunction is also implicated in excitoxic, neuronal injury, such as that associated with cerebrovascular accidents, seizures, and ischemia.

[0025] Some of the diseases disclosed herein, including the above diseases, appear to be caused by defects in Complex I of the respiratory chain. Electron transfer from Complex I to the remainder of the respiratory chain is mediated by the compound coenzyme Q (also known as Ubiquinoid). Oxidized coenzyme Q (CoQox or Ubiquinoid) is reduced by Complex I to reduced coenzyme Q (CoQred or Ubiquinol). The reduced coenzyme Q then transfers its electrons to Complex III of the respiratory chain, where it is re-oxidized to CoQox (Ubiquinoid). CoQox can then participate in further iterations of electron transfer.

[0026] Very few treatments are available for patients suffering from these mitochondrial diseases. The compound Idebenone has been proposed for treatment of Friedreich's Ataxia. While the clinical effects of Idebenone have been relatively modest, the complications of mitochondrial diseases can be so severe that even marginally useful therapies are preferable to the untreated course of the disease. Another compound, MitoQ, has been proposed for treating mitochondrial disorders (see U.S. Patent No. 7,179,928. Administration of coenzyme Q10 (CoQ10) and vitamin supplements have shown only transient beneficial effects in individual cases of KSS. CoQ10 supplementation has also been used for the treatment of CoQ10 deficiency with mixed results.

[0027] Oxidative stress is suspected to be important in neurodegenerative diseases such as Motor Neuron Disease, Amyotrophic Lateral Sclerosis (ALS), Creutzfeldt-Jakob disease, Machado-Joseph disease, Spino-cerebellar ataxia, Multiple sclerosis(MS), Parkinson's disease, Alzheimer's disease, and Huntington's disease. Oxidative stress is thought to be linked to certain cardiovascular disease and also plays a role in the ischemic cascade due to oxygen reperfusion injury following hypoxia. This cascade includes both strokes and heart attacks.

[0028] Damage accumulation theory, also known as the free radical theory of aging, invokes random effects of free radicals produced during aerobic metabolism that cause damage to DNA, lipids and proteins and accumulate over time. The concept of free radicals playing a role in the aging process was first introduced by Himan D (1956), Aging –A theory based on free-radical and radiation chemistry J. Gerontol. 11, 298-300.

[0029] According to the free radical theory of aging, the process of aging begins with oxygen metabolism (Valko et al, (2004) Role of oxygen radicals in DNA damage and cancer incidence, Mol. Cell. Biochem., 266, 37-56). Even under ideal conditions some electrons "leak" from the electron transport chain. These leaking electrons interact with oxygen to produce superoxide radicals, so that under physiological conditions, about 1-3% of the oxygen molecules in the mitochondria are converted into superoxide. The primary site of radical oxygen damage from superoxide radical is mitochondrial DNA (mtDNA) (Cadenas et al., (2000) Mitochondrial free radical generation, oxidative stress and aging, Free Radic. Res, 28, 601-609). The cell repairs much of the damage done to nuclear DNA (nDNA) but mtDNA repair seems to be less efficient. Therefore, extensive mtDNA damage accumulates over time and shuts down mitochondria causing cells to die and the organism to age.

[0030] Some of the diseases associated with aging (increasing age) are diabetes mellitus, hypertension, atherosclerosis, ischemia/reperfusion injury, rheumatoid arthritis, neurodegenerative disorders such as dementia, Alzheimer's, and Parkinson's. Diseases resulting from the process of aging as a physiological decline include decreases in muscle strength, cardiopulmonary function, vision, and hearing, as well as wrinkled skin and graying hair.

[0031] The ability to adjust biological production of energy has applications beyond the diseases described herein. Various other disorders can result in suboptimal levels of energy biomarkers (sometimes also referred to as indicators of energetic function), such as ATP

levels. Treatments for these disorders are also needed, in order to modulate one or more energy biomarkers to improve the health of the patient. In other applications, it can be desirable to modulate certain energy biomarkers away from their normal values in an individual that is not suffering from disease. In some embodiments, if an individual is undergoing an extremely strenuous undertaking, it can be desirable to raise the level of ATP in that individual.

[0032] While inflammation and oxidative stress define regimes which can have some overlapping areas, previous treatment of these regimes have typically entailed distinct treatments. More specifically, animals and humans with episodes of inflammation or oxidative stress in the liver have been treated with distinct protocols. Inflammation within the subjects has been treated with various anti-inflammatory compounds such as aspirin, ibuprofen, indomethacin and others. Oxidative stress within the subjects oftentimes will involve reducing the concentration of free radicals, as these free radicals are disruptive in reactions within cells, tissues, and organisms. The various mechanisms causing these episodes have not been viewed as having any common treatment approach, and to date, insights into mechanistic causes of these issues have not yet yielded any commonality in treatment.

[0033] There is thus a need for agents that can treat or suppress the adverse effects of inflammation and/or oxidative stress upon the liver in subjects. In particular, there is a need for agents that can treat or suppress the adverse effects of inflammation as well as oxidative stress, thereby simplifying and consolidating treatment.

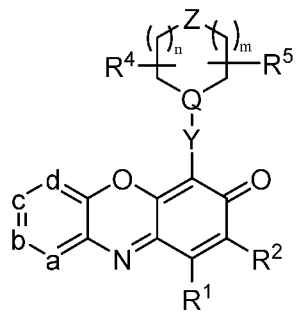
[0034] WO2009042270 discloses RecA inhibitors and uses as microbial inhibitors. WO2014070760 discloses resazurin and analogs thereof. EP0155623 discloses lipoxygenase inhibitors.

BRIEF SUMMARY OF THE INVENTION

[0035] The present disclosure provides, in some embodiments, compounds and compositions for treatment or suppression of diseases, developmental delays, and symptoms related to oxidative stress disorders; for treatment or suppression of liver and kidney disorders characterized by one or more inflammation and/or oxidative stress biomarkers, including but not limited to liver disorders resulting from SIRS, sepsis, severe illness, traumatic injury, and exposure to liver toxins; and for use in treating or suppression of injury

or damage caused by inflammation and/or oxidative stress in the liver or kidney. In some embodiments, such oxidative stress disorders include but are not limited to mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases, and diseases of aging.

[0036] In one aspect is a compound of Formula I:



(Formula I)

or the reduced form thereof; wherein: R^1 and R^2 are independently selected from the group consisting of H and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl, and wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -C(O)OH, -$NR^{25}R^{26}$, -O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl; a, b, c, and d are independently selected from the group consisting of –C(R^3)- and –N-, with the proviso that no more than three of a, b, c, and d are –N-; each R^3 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -CN, -C(O)OH, -$NR^{27}R^{28}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{15}R^{16}$, -O-C(O)-O-C_1-C_6 alkyl, -C(O)$NR^{29}R^{30}$, -S(O)$_2$-C_1-C_6 alkyl, -S(O)$_2$-$NR^{17}R^{18}$, -NHC(O)O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl, wherein each C_1-C_6 alkyl and -O-C_1-C_6 alkyl are independently optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -CN, -C(O)OH, -$NR^{31}R^{32}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{19}R^{20}$, -O-C(O)-O-C_1-C_6 alkyl, -C(O)NH_2, -S(O)$_2$-C_1-C_6 alkyl, -S(O)$_2$-$NR^{21}R^{22}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl; n and m are independently 0, 1, or 2; Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -OH, -CN, -C(O)OH, -$NR^{33}R^{34}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -S(O)$_2$-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, and 3 to 8-membered saturated heterocyclyl; R^4 and R^5 are independently

selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -CN, -C(O)OH, -$NR^{35}R^{36}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl; or R^4 and R^5 together with the intervening atom(s) form a 3-8 membered carbocylic or 3-8 membered heterocyclic ring, wherein the 3-8 membered carbocylic and 3-8 membered heterocyclic ring are optionally substituted with one or more substituents independently selected from the group consisting of –OH, -$NR^{37}R^{38}$, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and –O-C_1-C_6 alkyl; Q is N or CH; Z is –N(R^6)-, -C(R^7)(R^8)-, or –O-; R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)R^9, -C(O)OR^{10}, -C(O)N$R^{11}R^{12}$, -S(O)$_2$-C_1-C_6 alkyl, or -S(O)$_2$-N$R^{23}R^{24}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -C(O)OH, -N$R^{39}R^{40}$, -O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, and 3 to 8-membered saturated heterocyclyl; R^7 and R^8 are independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, and –N$R^{13}R^{14}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -C(O)OH, -NH_2, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl; or R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 haloalkyl, halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -OH, -C(O)OH, -NH_2, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl; R^9 is C_1-C_6 alkyl or C_1-C_6 haloalkyl; R^{10} is H or C_1-C_6 alkyl; R^{11} and R^{12} are independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring; R^{13} and R^{14} are independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, and R^{40} are independently selected from the group consisting of H and C_1-C_6 alkyl; or a salt, deuterated form, solvate, hydrate, stereoisomer, or mixture of stereoisomers thereof. In some embodiments, each R^3 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -C(O)OH, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -C(O)N$R^{29}R^{30}$, -S(O)$_2$-C_1-C_6 alkyl, -S(O)$_2$-N$R^{17}R^{18}$, -NHC(O)O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered

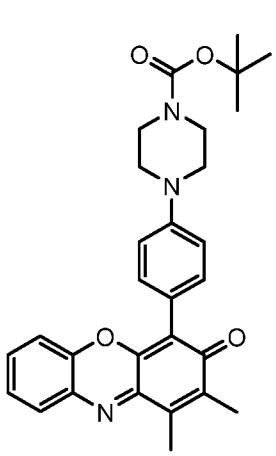
saturated heterocyclyl, and C_6-C_{10} aryl, wherein each C_1-C_6 alkyl is independently optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -CN, -C(O)OH, -$NR^{31}R^{32}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{19}R^{20}$, -O-C(O)-O-C_1-C_6 alkyl, -$C(O)NH_2$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{21}R^{22}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl. In some embodiments, each R^3 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -C(O)OH, -C(O)-C_1-C_6 alkyl, -$C(O)NR^{29}R^{30}$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{17}R^{18}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl, wherein each C_1-C_6 alkyl is independently optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -CN, -C(O)OH, -$NR^{31}R^{32}$, -C(O)-C_1-C_6 alkyl, -O-C(O)-$NR^{19}R^{20}$, -O-C(O)-O-C_1-C_6 alkyl, -$C(O)NH_2$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{21}R^{22}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl. In some embodiments, including any of the foregoing embodiments, R^3 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, wherein the "C_1-C_6 alkyl" is optionally substituted with one -OH. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl; a, b, c, and d are independently selected from the group consisting of -C(R^3)- and -N-, with the proviso that no more than three of a, b, c, and d are -N-; each R^3 is independently selected from the group consisting of H, halogen, unsubstituted C_1-C_6 alkyl, and C_1-C_6 haloalkyl; n and m are independently 0, 1, or 2; Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl; R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl; or R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocylic or 3-8 membered heterocyclic ring; Q is N or CH; Z is -N(R^6)-, -C(R^7)(R^8)-, or -O-; R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OR^{10}, or -C(O)-$NR^{11}R^{12}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more -OH; R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and -$NR^{13}R^{14}$; or R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from the group

consisting of C_1-C_6 haloalkyl, halogen, and C_1-C_6 alkyl; R^{10} is H or C_1-C_6 alkyl; R^{11} and R^{12} are independently selected from the group consisting of H and C_1-C_6 alkyl; or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring; and R^{13} and R^{14} are independently selected from the group consisting of H and C_1-C_6 alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are independently unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl; a, b, c, and d are independently selected from the group consisting of -C(R^3)- and -N-, with the proviso that no more than three of a, b, c, and d are -N-; each R^3 is independently selected from the group consisting of H and C_1-C_6 haloalkyl; n and m are independently 0, 1, or 2; Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl; R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl; or R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocylic or 3-8 membered unsubstituted heterocyclic ring; Q is N or CH; Z is –N(R^6)-, -C(R^7)(R^8)-, or -O-; R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OR^{10}, or -C(O)N$R^{11}R^{12}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more -OH; R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and -N$R^{13}R^{14}$; or R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from C_1-C_6 haloalkyl; R^{10} is C_1-C_6 alkyl; R^{11} and R^{12} are independently C_1-C_6 alkyl; and R^{13} and R^{14} are independently C_1-C_6 alkyl. In some embodiments, including any of the foregoing embodiments, Y is phenyl, optionally substituted with one or more substituents independently selected from C_1-C_6 alkyl; R^1 and R^2 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl; R^3 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, wherein the "C_1-C_6 alkyl" is optionally substituted with one -OH; and R^4 is selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH and halogen. In some embodiments, including any of the foregoing

embodiments, Y is phenyl, optionally substituted with one or more substituents independently selected from C_1-C_6 alkyl; R^1 and R^2 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl; and R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_3 alkyl. In some embodiments, including any of the foregoing embodiments, Y is phenyl substituted with one C_1 alkyl; R^1 and R^2 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl; and R^4 and R^5 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl. In some embodiments, including any of the foregoing embodiments, Y is phenyl substituted with one C_1 alkyl; R^1 and R^2 are $–CH_3$; and R^4 and R^5 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are unsubstituted C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is a linear or branched chain alkyl. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are $-CH_3$. In some embodiments, including any of the foregoing embodiments, R^1 and R^2 are methyl. In some embodiments, including any of the foregoing embodiments, a, b, c, and d are independently $-C(R^3)-$. In some embodiments, including any of the foregoing embodiments, b, c, and d are independently $–C(R^3)-$, and wherein a is -N-. In some embodiments, including any of the foregoing embodiments, each R^3 is H. In some embodiments, including any of the foregoing embodiments, b and d are -CH-, and wherein c is $-C(CF_3)-$. In some embodiments, including any of the foregoing embodiments, n and m are 1. In some embodiments, including any of the foregoing embodiments, n and m are 0. In some embodiments, including any of the foregoing embodiments, one of n and m is 1, and the other of n and m is 2. In some embodiments, including any of the foregoing embodiments, Y is phenyl substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl. In some embodiments, including any of the foregoing embodiments, Y is phenyl, optionally substituted with one or more substituents independently selected from C_1-C_6 alkyl. In some embodiments, including any of the foregoing embodiments, Y is phenyl is substituted with one C_1 alkyl. In some embodiments, including any of the foregoing embodiments, Y is unsubstituted phenyl. In some embodiments, including any of the foregoing embodiments, Y is unsubstituted pyridyl. In some embodiments, including any of

the foregoing embodiments, R^4 is selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH and halogen. In some embodiments, including any of the foregoing embodiments, R^4 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, wherein the "C_1-C_6 alkyl" is optionally substituted with one -OH; and R^5 is selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH and halogen. In some embodiments, including any of the foregoing embodiments, R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_3 alkyl. In some embodiments, R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1 alkyl. In some embodiments, including any of the foregoing embodiments, R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl. In some embodiments, including any of the foregoing embodiments, R^4 and R^5 are H. In some embodiments, including any of the foregoing embodiments, R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocyclic ring. In some embodiments, including any of the foregoing embodiments, R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted heterocyclic ring. In some embodiments, including any of the foregoing embodiments, Q is N. In some embodiments, including any of the foregoing embodiments, Q is CH. In some embodiments, including any of the foregoing embodiments, Z is -N(R^6)-. In some embodiments, including any of the foregoing embodiments, Z is -C(R^7)(R^8)-. In some embodiments, including any of the foregoing embodiments, Z is -O-. In some embodiments, including any of the foregoing embodiments, R^6 is H. In some embodiments, including any of the foregoing embodiments, R^6 is C_1-C_6 alkyl substituted with one or more -OH. In some embodiments, including any of the foregoing embodiments, R^6 is unsubstituted C_1-C_6 alkyl. In some embodiments, including any of the foregoing embodiments, R^6 is C_1-C_6 haloalkyl. In some embodiments, including any of the foregoing embodiments, R^6 is -C(O)OR^{10}. In some embodiments, including any of the foregoing embodiments, R^6 is -C(O)$NR^{11}R^{12}$. In some embodiments, including any of the foregoing embodiments, R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and –$NR^{13}R^{14}$. In some embodiments, including any of the foregoing embodiments, R^7 and R^8 together with the carbon atom to which they are attached

form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from C_1-C_6 haloalkyl. In some embodiments, including any of the foregoing embodiments, the compound is selected from the group consisting of: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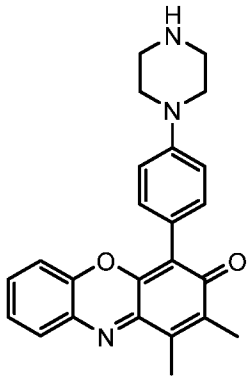
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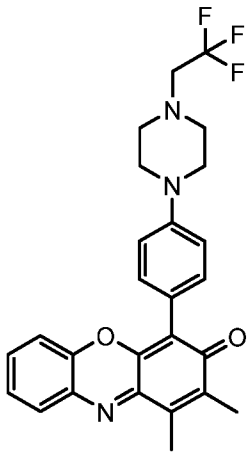
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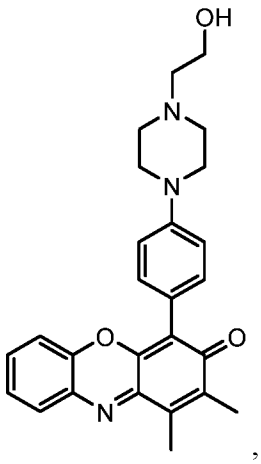
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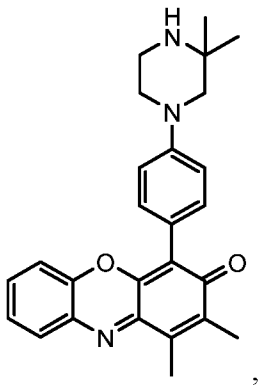
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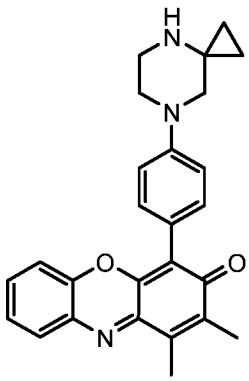
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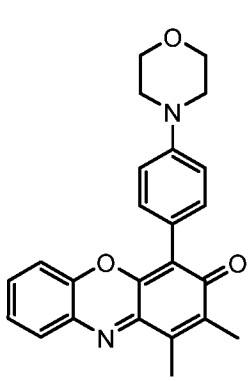
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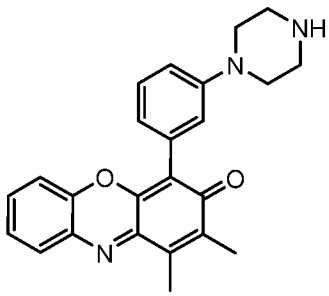
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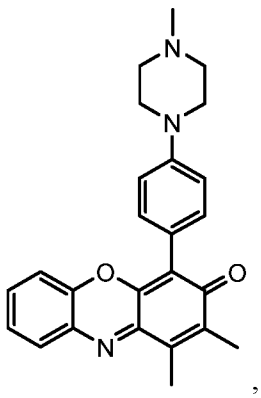
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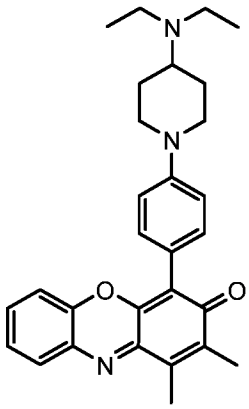
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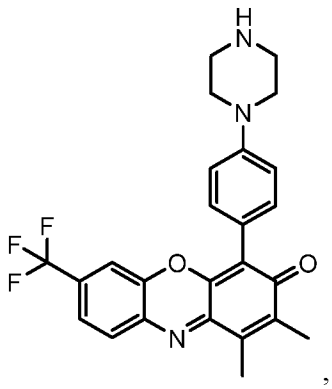
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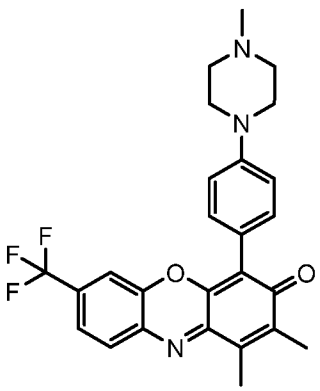
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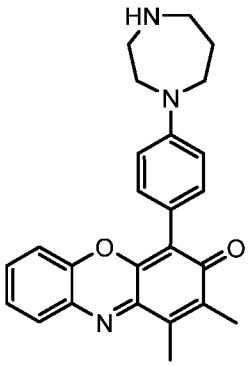
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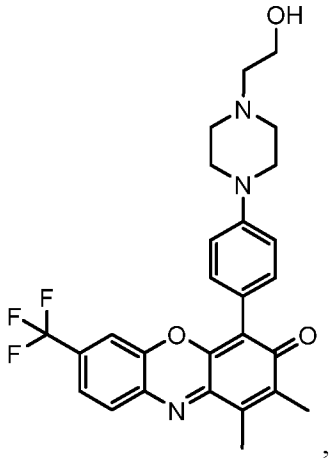
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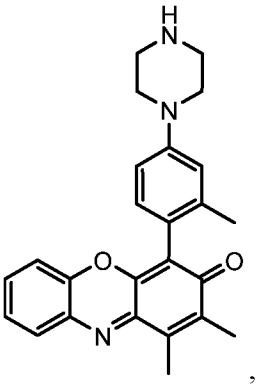
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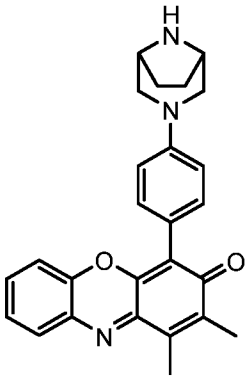
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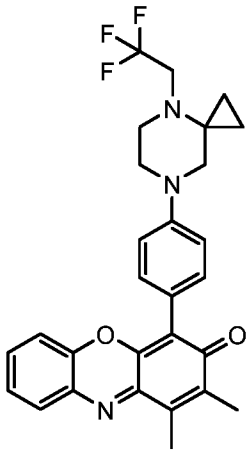
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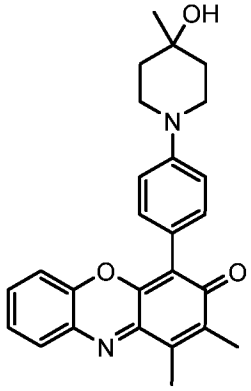
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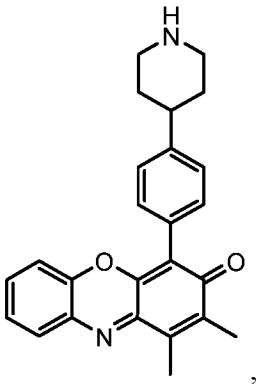
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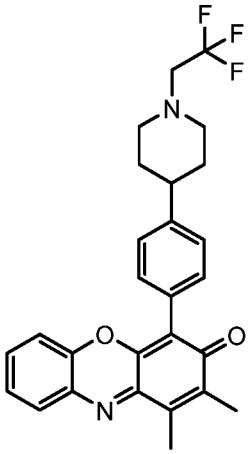
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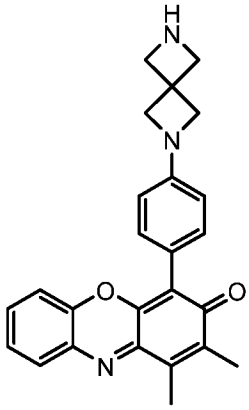
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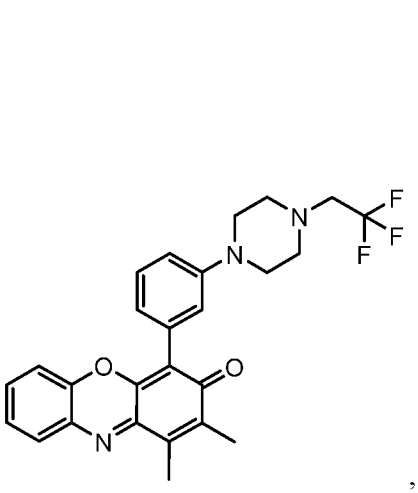
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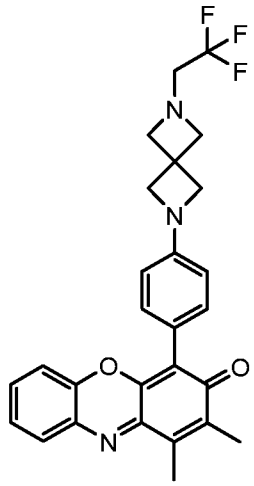
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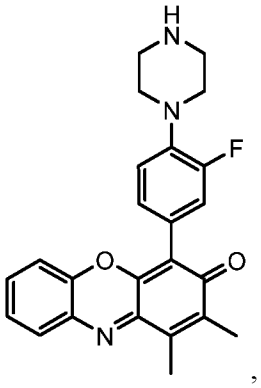
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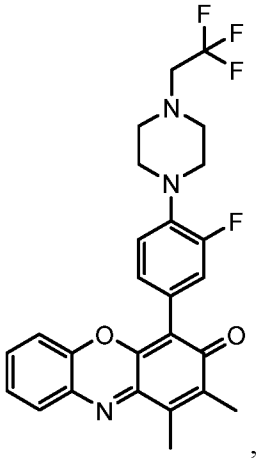
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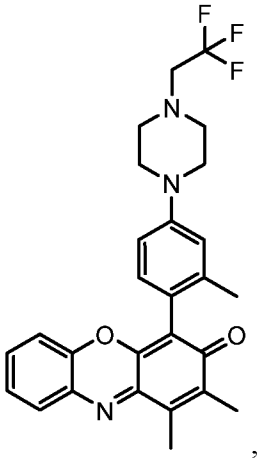
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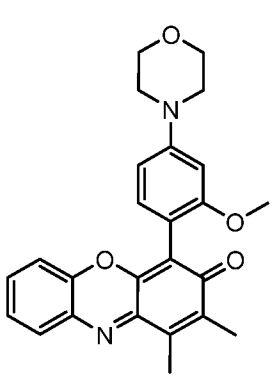
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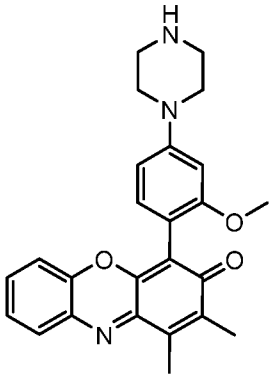
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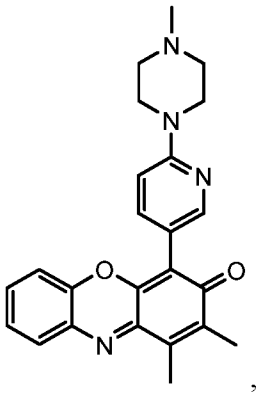
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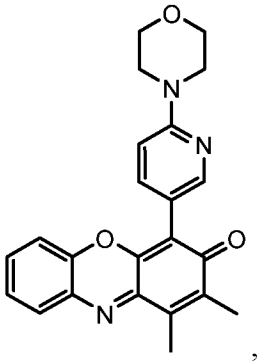
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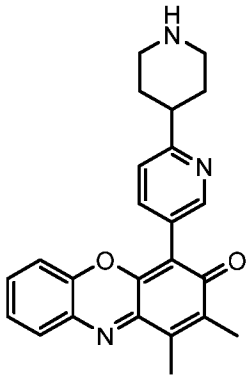
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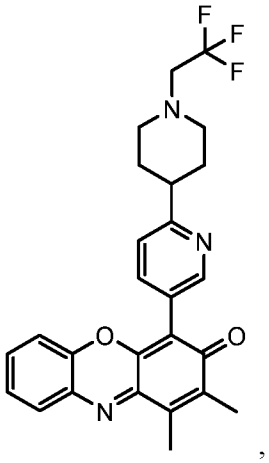
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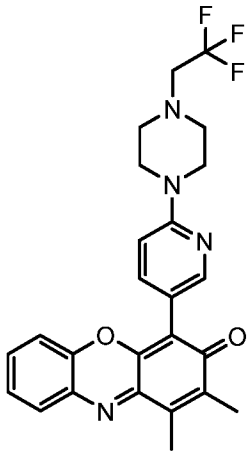
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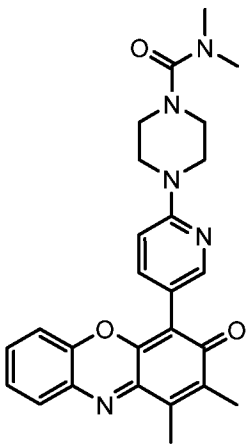
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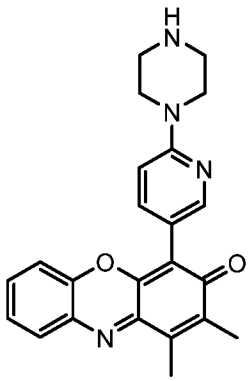
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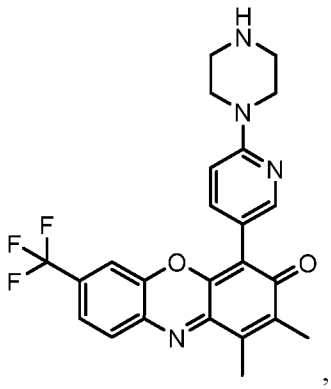
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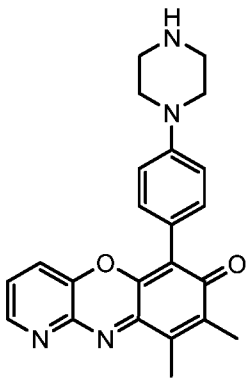
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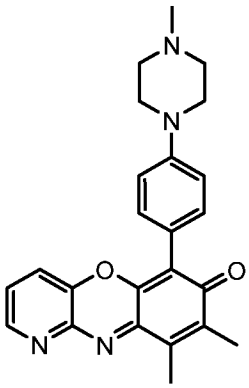
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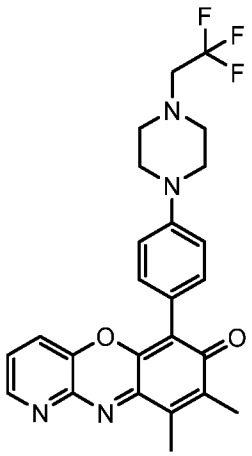
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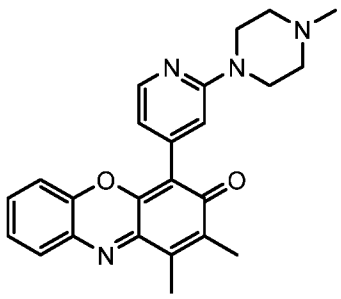
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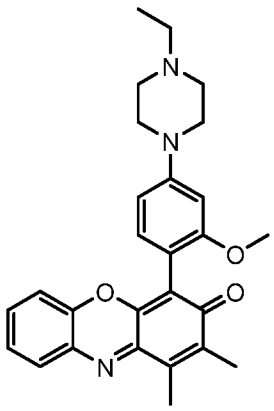
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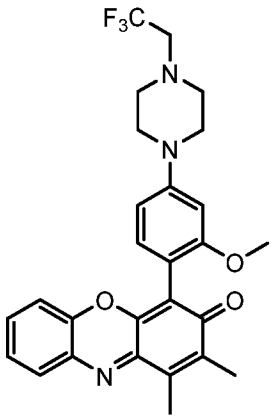
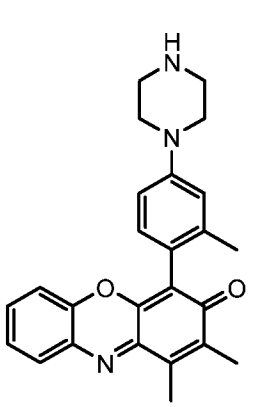
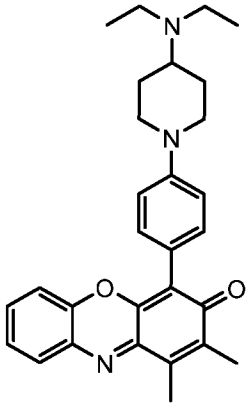
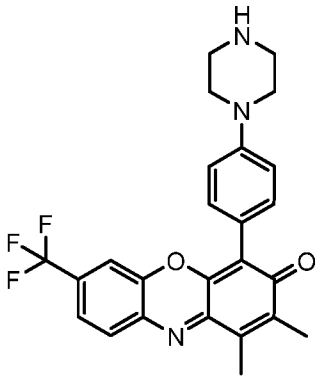
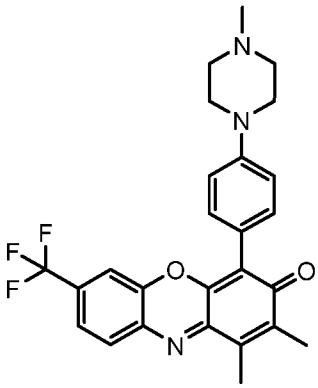
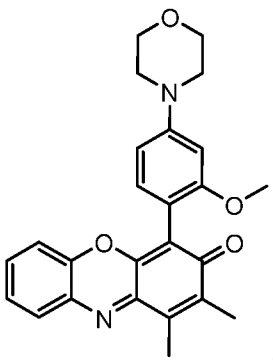
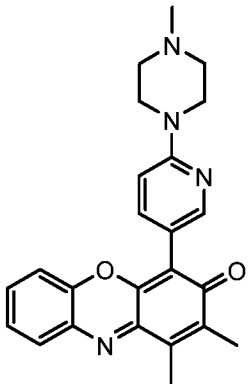
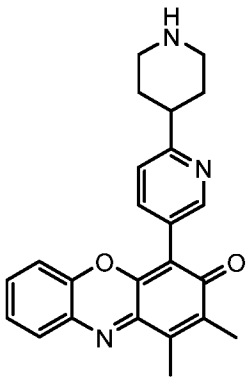

; or the reduced form thereof; or a salt, deuterated form, solvate, hydrate, stereoisomer, or mixture of stereoisomers thereof. In some embodiments, the compound is selected from the group

consisting of:  ,  ,  ,  ,  ,  , and  ; or the reduced form thereof; or a salt, deuterated form, solvate, or hydrate thereof. In some embodiments, including any of the foregoing embodiments, the compound is in the oxidized form. In some embodiments, including any of the foregoing embodiments, the compound is in the reduced form. In some embodiments, including any of the foregoing embodiments, the compound is not a salt. In some embodiments, including any of the foregoing embodiments, the compound is a pharmaceutically acceptable salt.

[0037] In another aspect is a pharmaceutical composition comprising a compound as described herein (including but not limited to a compound described in the immediately preceding paragraph) and a pharmaceutically acceptable carrier, pharmaceutically acceptable

excipient, or pharmaceutically acceptable vehicle. In some embodiments, including any of the foregoing embodiments, a pharmaceutical composition comprises a compound as described herein (including but not limited to a compound described in the immediately preceding paragraph) and a pharmaceutically acceptable carrier. In another aspect is a pharmaceutical composition comprising an active agent and a pharmaceutically acceptable carrier, wherein the active agent consists of, or consists essentially of, a compound as described herein (including but not limited to a compound described in the immediately preceding paragraph). Any one or more of the compounds described herein, including all of the foregoing compounds, can be formulated into a unit dose formulation. In some embodiments, including any of the foregoing embodiments, the pharmaceutical composition further comprises an additional material selected from the group consisting of omega-3 fatty acids (also referred to as n-3 polyunsaturated fatty acids or n-3 PUFA), such as docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA); CoQ10; and N-acetyl cysteine (NAC). In some embodiments, including any of the foregoing embodiments, the additional agent is selected from the group consisting of docosahexaenoic acid, eicosapentaenoic acid, CoQ10, and n-acetyl cysteine. In some embodiments, including any of the foregoing embodiments, the additional agent has a weight % concentration of 1-99% based on the total weight of the compound and the additional material.

[0038] In another aspect is a method of treating or suppressing an oxidative stress disorder, treating or suppressing a liver or kidney disorder, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, comprising administering to a subject in need thereof a therapeutically effective amount, a prophylactically effective amount, or effective amount of a compound or composition (in some embodiments a pharmaceutical composition) as described herein (including but not limited to a compound described in the paragraph preceding the above paragraph), where, in some embodiments, when the compound is a salt, the salt is a pharmaceutically acceptable salt. In another embodiment is a method of treating or suppressing an oxidative stress disorder, treating or suppressing a liver or kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, comprising administering to a subject in need thereof a therapeutically effective amount, a prophylactically effective amount, or effective amount of a compound or composition (in

some embodiments a pharmaceutical composition) as described herein (including but not limited to a compound described in the paragraph preceding the above paragraph), where, in some embodiments, when the compound is a salt, the salt is a pharmaceutically acceptable salt. In another embodiment is a method of treating or suppressing an oxidative stress disorder, treating or suppressing a liver or kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers present in an abnormal amount, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, comprising administering to a subject in need thereof a therapeutically effective amount, a prophylactically effective amount, or effective amount of a compound or composition (in some embodiments a pharmaceutical composition) as described herein (including but not limited to a compound described in the paragraph preceding the above paragraph), where, in some embodiments, when the compound is a salt, the salt is a pharmaceutically acceptable salt. In some embodiments, including any of the foregoing embodiments, the abnormal amount of the one or more inflammation and/or oxidative stress biomarkers is at least one standard deviation away from the respective control level, at least two standard deviations away from the respective control level, or at least three standard deviations away from the respective control level; wherein the control level is an age-matched control level, a sex-matched control level, a smoker-status matched control level, and/or a healthy control level (a control level of a patient which does not have the disease or disorder). In some embodiments, including any of the foregoing embodiments, a therapeutically effective amount of the compound or composition (in some embodiments a pharmaceutical composition) as described herein is administered. In some embodiments, including any of the foregoing embodiments, a prophylactically effective amount of the compound or composition (in some embodiments a pharmaceutical composition) as described herein is administered. In some embodiments, including any of the foregoing embodiments, an effective amount of the compound or composition (in some embodiments a pharmaceutical composition) as described herein is administered. The method can use any individual compound as described herein, or a combination of compounds. In some embodiments, including any of the foregoing embodiments, the compound is administered as a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier. In some embodiments, including any of the foregoing embodiments, the pharmaceutical composition comprises an active agent consisting essentially of the

compound, and a pharmaceutically acceptable carrier. In some embodiments of the method, including any of the foregoing embodiments, administering the compound is done orally, in some embodiments, with a pharmaceutical composition, medical food, or ingestible supplement. In some embodiments of the method, including any of the foregoing embodiments, administering the compound is done via injection. In some embodiments of the method, including any of the foregoing embodiments, administering the compound is done topically. In some embodiments of the method, including any of the foregoing embodiments, administering the compound is done in conjunction with a member of the group consisting of omega-3 fatty acids (also referred to as n-3 polyunsaturated fatty acids or n-3 PUFA), such as docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA), as well as CoQ10 and n-acetyl cysteine (NAC), and the member has a weight % concentration of 1-99% based on the combined weight of the compound and co-administered material. In some embodiments of the method, including any of the foregoing embodiments, the subject is a eukaryotic system. In some embodiments of the method, including any of the foregoing embodiments, the subject is a human. In some embodiments of the method, including any of the foregoing embodiments, the subject is a human subject and the administering comprises about 0.5 mg to about 10 mg/kg; about 1 mg to about 8 mg/kg; about 1 mg to about 5 mg of the compound per kg of body weight. In some embodiments, the method is a method of treating or suppressing an oxidative stress disorder selected from the group consisting of: a mitochondrial disorder; an inherited mitochondrial disease; Alpers Disease; Barth syndrome; a Beta-oxidation Defect; Carnitine-Acyl-Carnitine Deficiency; Carnitine Deficiency; a Creatine Deficiency Syndrome; Co-Enzyme Q10 Deficiency; Complex I Deficiency; Complex II Deficiency; Complex III Deficiency; Complex IV Deficiency; Complex V Deficiency; COX Deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I Deficiency; CPT II deficiency; Friedreich's Ataxia (FA); Glutaric Aciduria Type II; Kearns-Sayre Syndrome (KSS); Lactic Acidosis; Long-Chain Acyl-CoA Dehydrongenase Deficiency (LCAD); LCHAD; Leigh Syndrome; Leigh-like Syndrome; Leber's Hereditary Optic Neuropathy (LHON); Lethal Infantile Cardiomyopathy (LIC); Luft Disease; Multiple Acyl-CoA Dehydrogenase Deficiency (MAD); Medium-Chain Acyl-CoA Dehydrongenase Deficiency (MCAD); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS); Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Recessive Ataxia Syndrome (MIRAS); Mitochondrial Cytopathy, Mitochondrial DNA Depletion;

Mitochondrial Encephalopathy; Mitochondrial Myopathy; Myoneurogastointestinal Disorder and Encephalopathy (MNGIE); Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP); Pearson Syndrome; Pyruvate Carboxylase Deficiency; Pyruvate Dehydrogenase Deficiency; a POLG Mutation; a Respiratory Chain Disorder; Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD); SCHAD; Very Long-Chain Acyl-CoA Dehydrongenase Deficiency (VLCAD); a myopathy; cardiomyopathy; encephalomyopathy; a neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); a motor neuron disease; a neurological disease; epilepsy; a disease associated with aging; macular degeneration; diabetes; metabolic syndrome; a genetic disease; Huntington's Disease; a mood disorder; schizophrenia; bipolar disorder; a pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett's disorder; PDD-not otherwise specified (PDD-NOS); a cerebrovascular accident; stroke; a vision impairment; optic neuropathy; dominant inherited juvenile optic atrophy; optic neuropathy caused by a toxic agent; glaucoma; Stargardt's macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemic reperfusion related retinal injury; oxygen poisoning; a haemoglobionopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit/hyperactivity disorder (ADHD); a neurodegenerative disorder resulting in hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally inherited diabetes and deafness (MIDD); chronic fatigue; contrast-induced kidney damage; contrast-induced retinopathy damage; Abetalipoproteinemia; retinitis pigmentosum; Wolfram's disease; Tourette syndrome; cobalamin c defect; methylmalonic aciduria; glioblastoma; Down's syndrome; acute tubular necrosis; a muscular dystrophy; a leukodystrophy; Progressive Supranuclear Palsy; spinal muscular atrophy; hearing loss; noise induced hearing loss; traumatic brain injury; Juvenile Huntington's Disease; Multiple Sclerosis; NGLY1; Multisystem atrophy; Adrenoleukodystrophy; and Adrenomyeloneuropathy. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is a mitochondrial disorder. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is an inherited mitochondrial disease. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Friedreich's Ataxia (FA). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Kearns-Sayre Syndrome (KSS). In some embodiments, including any of the foregoing

embodiments, the oxidative stress disorder is Leigh Syndrome, or Leigh-like Syndrome. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Leber's Hereditary Optic Neuropathy (LHON). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Myoclonic Epilepsy with Ragged Red Fibers (MERRF). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Parkinson's disease. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Alzheimer's disease. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is amyotrophic lateral sclerosis (ALS). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is epilepsy. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is macular degeneration. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Huntington's Disease. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is autistic disorder. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Rett's disorder. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is stroke. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is Maternally inherited diabetes and deafness (MIDD). In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is chronic fatigue. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is contrast-induced kidney damage. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is contrast-induced retinopathy damage. In some embodiments, including any of the foregoing embodiments, the oxidative stress disorder is cobalamin c defect. In some embodiments, including any of the foregoing embodiments, the method is for treating the oxidative stress disorder. In some embodiments, including any of the foregoing embodiments, the method is for suppressing the oxidative stress disorder. In some embodiments, including any of the foregoing embodiments, the compound is used in a method of treating or suppressing a liver disorder characterized by one or more inflammation and/or oxidative stress biomarkers. In some embodiments, including any of the foregoing embodiments, the compound is used in a method of treating or

suppressing a liver disorder characterized by one or more inflammation and/or oxidative stress biomarkers wherein the one or more inflammation and/or oxidative stress biomarkers is selected from the group consisting of transaminase (alanine transaminase (ALT), aspartate amino transferase (AST)), and 4-hydroxynonenal (4-HNE). In some embodiments, including any of the foregoing embodiments, the enzyme activity is quantified in plasma and the 4-HNE is quantified in liver lysates. In some embodiments, including any of the foregoing embodiments, 4-HNE is normalized to input protein concentrations. In some embodiments, including any of the foregoing embodiments, the liver disorder is selected from the group consisting of nonalcoholic fatty liver (NAFL), Nonalcoholic steatohepatitis (NASH), alcoholic hepatitis, cholestatic liver disease, viral hepatitis, drug-induced liver toxicity, hemochromatosis, Wilson's disease, transplant reperfusion injury, and hepatic insufficiency. In some embodiments, the hepatic insufficiency is caused by traumatic injury, systemic inflammatory response syndrome (SIRS), sepsis, and/or severe illness. In some embodiments, including any of the foregoing embodiments, the compound is used in a method of treating or suppressing a kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers. In some embodiments, the kidney disorder is kidney insufficiency caused by traumatic injury and/or illness. In some embodiments of the method, including any of the foregoing embodiments, the mode of action associated with inflammation and oxidative stress is similar for the liver and kidney. In some embodiments, including any of the foregoing embodiments, the method is for treating or suppressing injury or damage caused by inflammation and/or oxidative stress of the liver, comprising administering to a cell or cells, a tissue or tissues, or a subject in need thereof, a therapeutically effective amount or a prophylactically effective amount of a compound or composition disclosed herein. In some embodiments, including any of the foregoing embodiments, the method is for treating or suppressing a liver disorder. In some embodiments, including any of the foregoing embodiments, the compound is used therapeutically during, after, or during and after exposure to a factor which may result in inflammation and/or oxidative stress, by administering a therapeutically effective amount to a subject in need thereof. In some embodiments, including any of the foregoing embodiments, the compound is used prophylactically prior to, or in conjunction with, exposure to a factor which may result in levels of one or more biomarkers indicating inflammation and/or oxidative stress, by administering a prophylactically effective amount to a subject in need (or potential need)

thereof. In some embodiments, the one or more compounds are administered concurrently with onset of inflammation and/or oxidative stress. In some embodiments, including any of the foregoing embodiments, the one or more compounds are administered after onset of inflammation and/or oxidative stress. In some embodiments, including any of the foregoing embodiments, the method further comprises administering an additional agent wherein the additional agent is selected from the group consisting of omega-3 fatty acids, CoQ10, and N-acetyl cysteine (NAC). In some embodiments, including any of the foregoing embodiments, the method comprises administering an additional agent selected from the group consisting of NAC and DHA. In some embodiments, including any of the foregoing embodiments, the method comprises administering an additional agent which has a weight % concentration of 1-99% based on the total weight of the compound and additional agent.

[0039] In some embodiments, including any of the foregoing embodiments, the method is a method for modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, wherein an effective amount of the compound or composition (in some embodiments a pharmaceutical composition) as described herein is administered and wherein the one or more energy biomarkers are selected from the group consisting of: lactic acid (lactate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; pyruvic acid (pyruvate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; lactate/pyruvate ratios, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized glutathione levels, or reduced/oxidized glutathione ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized cysteine levels, or reduced/oxidized cysteine ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; phosphocreatine levels, NADH (NADH + H^+) levels; NADPH (NADPH + H^+) levels; NAD levels; NADP levels; ATP levels; reduced coenzyme Q (CoQred) levels; oxidized coenzyme Q (CoQox) levels; total coenzyme Q (CoQtot) levels; oxidized cytochrome C levels; reduced cytochrome C levels; oxidized cytochrome C/reduced cytochrome C ratio; acetoacetate levels, b-hydroxy butyrate levels, acetoacetate/b-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; levels of reactive oxygen species; levels of oxygen consumption (VO_2); levels of carbon dioxide output (VCO_2); respiratory quotient (VCO_2/VO_2); exercise tolerance; and anaerobic threshold. In some embodiments, including any of the foregoing embodiments, the

levels are modulated to a value within about 2 standard deviations of the value in a healthy subject. In some embodiments, including any of the foregoing embodiments, the levels are modulated to a value within about 1 standard deviation of the value in a healthy subject. In some embodiments, including any of the foregoing embodiments, the levels in a subject are changed by at least about 10% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 20% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 30% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 40% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 50% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 75% above or below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the levels are changed by at least about 100% above or at least about 90% below the level in the subject prior to modulation. In some embodiments, including any of the foregoing embodiments, the subject or subjects in which a method of treating or suppressing an oxidative stress disorder, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers is performed is/are selected from the group consisting of subjects undergoing strenuous or prolonged physical activity; subjects with chronic energy problems; subjects with chronic respiratory problems; pregnant females; pregnant females in labor; neonates; premature neonates; subjects exposed to extreme environments; subjects exposed to hot environments; subjects exposed to cold environments; subjects exposed to environments with lower-than-average oxygen content; subjects exposed to environments with higher-than-average carbon dioxide content; subjects exposed to environments with higher-than-average levels of air pollution; airline travelers; flight attendants; subjects at elevated altitudes; subjects living in cities with lower-than-average air quality; subjects working in enclosed environments where air quality is degraded; subjects with lung diseases; subjects with lower-than-average lung capacity; tubercular patients; emphysema patients; cystic fibrosis patients; subjects recovering from surgery; subjects recovering from illness; elderly subjects; elderly subjects experiencing decreased

energy; subjects suffering from chronic fatigue; subjects suffering from chronic fatigue syndrome; subjects undergoing acute trauma; subjects in shock; subjects requiring acute oxygen administration; subjects requiring chronic oxygen administration; subjects requiring organ visualization via contrast solution; or other subjects with acute, chronic, or ongoing energy demands who can benefit from enhancement of energy biomarkers.

[0040] In some embodiments, including any of the foregoing embodiments, the disclosure embraces a method using a therapeutically effective amount or a prophylactically effective amount of a compound or composition described herein. In some embodiments, including any of the foregoing embodiments, the disclosure embraces a method using a therapeutically effective amount of a compound or composition described herein. In some embodiments, including any of the foregoing embodiments, the disclosure embraces a method using a prophylactically effective amount of a compound or composition described herein.

[0041] In some embodiments, including any of the foregoing embodiments, the disclosure embraces a method of mitigating inflammation and/or oxidative stress in a subject comprising: administering a compound described herein (including any of the foregoing embodiments) to the subject experiencing inflammation and/or oxidative stress.

[0042] The compounds described herein may also be used in a method of increasing the therapeutic window of a drug that has potentially toxic effects due to its ability to cause inflammation and/or oxidative stress in a tissue. For example, certain drugs, such as acetaminophen, can be toxic for the liver above certain doses. By co-administering one or more compounds described herein in conjunction with the drug, either in the same composition or as separate compositions, the drug may safely be administered at higher doses.

[0043] The compounds described herein may also be administered in combination with an active agent that may cause inflammation and/or oxidative stress. In such cases, the amount of the active agent may be increased when co-administered with a compound described herein (i.e. its therapeutic window is increased as a function of co-administration with a compound described herein). Co-administration includes administration of both the compound and the other active agent in a single composition, or as separate compositions. When administered as separate compositions they may be administered simultaneously, or on different dosing schedules (e.g. one composition may be administered daily, and the other administered twice daily).

[0044] In general, the compounds are described herein are in their oxidized form. For all the embodiments, compounds, compositions, formulations and methods described herein, the reduced form of the compounds may be used where desired. .

[0045] A "compound as described herein" includes reference to the compounds described herein as well as derivatives described herein.

[0046] For the compounds, compositions, formulations, and methods of treatment described herein include "comprising", "consisting of", and "consisting essentially of" embodiments. In some embodiments, for all compositions described herein, and all methods using a composition described herein, the compositions and methods can either comprise the listed components or steps, or can "consist essentially of" the listed components or steps. When a composition is described as "consisting essentially of" the listed components, the composition contains the components listed, and may contain other components which do not substantially affect the condition being treated, but do not contain any other components which substantially affect the condition being treated other than those components expressly listed; or, if the composition does contain extra components other than those listed which substantially affect the condition being treated, the composition does not contain a sufficient concentration or amount of the extra components to substantially affect the condition being treated. When a method is described as "consisting essentially of" the listed steps, the method contains the steps listed, and may contain other steps that do not substantially affect the condition being treated, but the method does not contain any other steps which substantially affect the condition being treated other than those steps expressly listed. As a non-limiting specific example, when a composition is described as 'consisting essentially of' a component, the composition may additionally contain any amount of pharmaceutically acceptable carriers, vehicles, or diluents and other such components which do not substantially affect the condition being treated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] **Figure 1** illustrates Study 1 plasma AST enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0048] **Figure 2** illustrates Study 2 plasma AST enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0049] **Figure 3** illustrates Study 1 plasma ALT enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0050] **Figure 4** illustrates Study 2 plasma ALT enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0051] **Figure 5** illustrates Study 1 liver 4-HNE lysate levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0052] **Figure 6** illustrates Study 2 liver 4-HNE lysate levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0053] **Figure 7** illustrates Study 3 plasma AST enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compound.

[0054] **Figure 8** illustrates Study 3 plasma ALT enzyme levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compound.

[0055] **Figure 9** illustrates Study 3 liver 4-HNE lysate levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compound.

[0056] **Figure 10** illustrates GSH levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction in the presence of distinct dosing levels of the test compounds.

[0057] **Figure 11** illustrates Isoprostane/Creatinine levels taken 4 hours after treatment, for a control, APAP introduction, and APAP introduction at a single dosing level of the test compound.

[0058] **Figure 12** illustrates plasma AST enzyme levels taken 4 hours after treatment, for a control, BSO introduction, and BSO introduction in the presence of distinct dosing levels of the test compound.

[0059] **Figure 13** illustrates plasma ALT enzyme levels taken 4 hours after treatment, for a control, BSO introduction, and BSO introduction in the presence of distinct dosing levels of the test compound.

INCORPORATION BY REFERENCE

[0060] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0061] Co-assigned U.S. Provisional Application No. 62/443,641, titled "ARYL- AND HETEROARYL- RESORUFIN DERIVATIVES FOR TREATMENT OF OXIDATIVE STRESS DISORDERS" filed on January 6, 2017 is incorporated by reference herein in its entirety.

DETAILED DESCRIPTION

[0062] Provided herein are compounds useful in treating or suppressing diseases, developmental delays and symptoms related to oxidative stress such as mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases and diseases of aging, and methods of using such compounds for treating or suppressing an oxidative stress disorder, or for modulating, normalizing, or enhancing one or more (e.g. one, two, three, or more) energy biomarkers.

[0063] The abbreviations used herein have their conventional meaning within the chemical and biological arts, unless otherwise specified.

[0064] Reference to "about" a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0065] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with temperatures, doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent.

Specifically, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 15%, within 10%, within 5%, within 4%, within 3%, within 2%, within 1%, or within 0.5% of the specified dose, amount, or weight percent.

[0066] The terms "a" or "an," as used in herein means one or more, unless context clearly dictates otherwise.

[0067] By "subject," "individual," or "patient" is meant an individual eukaryotic organism, preferably a vertebrate, more preferably a mammal, most preferably a human. In some embodiments, subject means a vertebrate. In some embodiments, subject means a mammal. In some embodiments, subject means a human.

[0068] "Treating" a disorder with the compounds and methods discussed herein is defined as administering one or more of the compounds discussed herein, with or without additional therapeutic agents, in order to reduce or eliminate either the disorder or one or more symptoms of the disorder, or to retard the progression of the disorder or of one or more symptoms of the disorder, or to reduce the severity of the disorder or of one or more symptoms of the disorder. "Suppressing" a disorder with the compounds and methods discussed herein is defined as administering one or more of the compounds discussed herein, with or without additional therapeutic agents, in order to suppress the clinical manifestation of the disorder, or to suppress the manifestation of adverse symptoms of the disorder. The distinction between treatment and suppression is that treatment occurs after adverse symptoms of the disorder are manifest in a subject, while suppression occurs before adverse symptoms of the disorder are manifest in a subject. Suppression may be partial, substantially total, or total. In some embodiments, genetic screening can be used to identify patients at risk of the disorder. The compounds and methods disclosed herein can then be administered to asymptomatic patients at risk of developing the clinical symptoms of the disorder, in order to suppress the appearance of any adverse symptoms.

[0069] "Therapeutic use" of the compounds discussed herein is defined as using one or more of the compounds discussed herein to treat or suppress a disorder, as defined herein. An "effective amount" of a compound is an amount of the compound sufficient to modulate, normalize, or enhance one or more energy biomarkers (where modulation, normalization, and enhancement are defined below). A "therapeutically effective amount" of a compound is an amount of the compound, which, when administered to a subject, is sufficient to reduce or eliminate either a disorder or one or more symptoms of a disorder, or to retard the

progression of a disorder or of one or more symptoms of a disorder, or to reduce the severity of a disorder or of one or more symptoms of a disorder, or to suppress the clinical manifestation of a disorder, or to suppress the manifestation of adverse symptoms of a disorder. A therapeutically effective amount can be given in one or more administrations. An "effective amount" of a compound embraces a therapeutically effective amount, a prophylactically effective amount, as well as an amount effective to modulate, normalize, or enhance one or more energy biomarkers in a subject. A "prophylactically effective amount" of a compound is an amount of the compound, which, when administered to a subject prior to exposure to a factor which may result in inflammation and/or oxidative stress, is sufficient to prevent one or more deleterious effects of inflammation and/or oxidative stress, or the clinical manifestation of inflammation and/or oxidative stress, or to prevent the manifestation of one or more adverse symptoms of inflammation and/or oxidative stress. A prophylactically effective amount can be given in one or more administrations.

[0070] "Prophylactic use" of the compounds discussed herein is defined as using one or more of the compounds discussed herein as a prophylaxis against inflammation and/or oxidative stress (*e.g.* to prevent the deleterious effects of inflammation and/or oxidative stress or one or more symptoms of inflammation and/or oxidative stress) prior to exposure to factors which may result in inflammation and/or oxidative stress. Prophylactic use of the compounds and methods described herein would include, in some embodiments, administering one or more of the compounds described herein to patients undergoing a medical treatment which may damage or injure a patient, in some embodiments to the patient's liver or kidney, where the compound or compounds are administered prior to the medical treatment. Prevention includes complete prevention as well as partial prevention.

[0071] "Modulation" of, or to "modulate," an energy biomarker means to change the level of the energy biomarker towards a desired value, or to change the level of the energy biomarker in a desired direction (e.g., increase or decrease). Modulation can include, but is not limited to, normalization and enhancement as defined below.

[0072] "Normalization" of, or to "normalize," an energy biomarker is defined as changing the level of the energy biomarker from a pathological value towards a normal value, where the normal value of the energy biomarker can be 1) the level of the energy biomarker in a healthy person or subject, or 2) a level of the energy biomarker that alleviates one or more undesirable symptoms in the person or subject. That is, to normalize an energy biomarker

which is depressed in a disease state means to increase the level of the energy biomarker towards the normal (healthy) value or towards a value which alleviates an undesirable symptom; to normalize an energy biomarker which is elevated in a disease state means to decrease the level of the energy biomarker towards the normal (healthy) value or towards a value which alleviates an undesirable symptom.

[0073] "Enhancement" of, or to "enhance," energy biomarkers means to intentionally change the level of one or more energy biomarkers away from either the normal value, or the value before enhancement, in order to achieve a beneficial or desired effect. In some embodiments, in a situation where significant energy demands are placed on a subject, it may be desirable to increase the level of ATP in that subject to a level above the normal level of ATP in that subject. Enhancement can also be of beneficial effect in a subject suffering from a disease or pathology such as e.g. a mitochondrial disorder, in that normalizing an energy biomarker may not achieve the optimum outcome for the subject; in such cases, enhancement of one or more energy biomarkers can be beneficial, in some embodiments, higher-than-normal levels of ATP, or lower-than-normal levels of lactic acid (lactate) can be beneficial to such a subject.

[0074] By modulating, normalizing, or enhancing the energy biomarker Coenzyme Q is meant modulating, normalizing, or enhancing the variant or variants of Coenzyme Q which is predominant in the species of interest. In some embodiments, the variant of Coenzyme Q which predominates in humans is Coenzyme Q10. If a species or subject has more than one variant of Coenzyme Q present in significant amounts (i.e., present in amounts which, when modulated, normalized, or enhanced, can have a beneficial effect on the species or subject), modulating, normalizing, or enhancing Coenzyme Q can refer to modulating, normalizing or enhancing any or all variants of Coenzyme Q present in the species or subject.

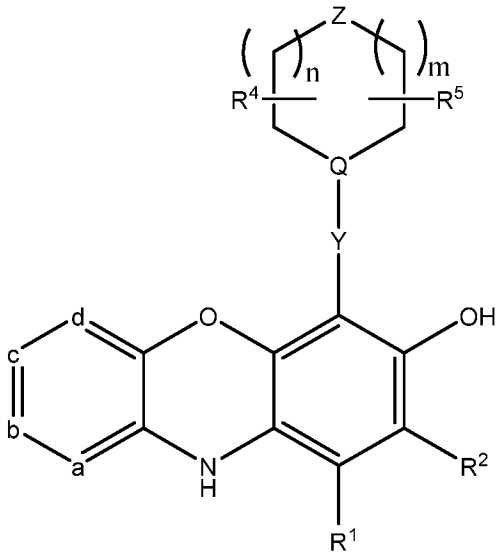
[0075] While the compounds described herein can occur and can be used as the neutral (non-salt) compound, the description is intended to embrace all salts of the compounds described herein, as well as methods of using such salts of the compounds. In some embodiments, the salts of the compounds comprise pharmaceutically acceptable salts. Pharmaceutically acceptable salts are those salts which can be administered as drugs or pharmaceuticals to humans and/or animals and which, upon administration, retain at least some of the biological activity of the free compound (neutral compound or non-salt compound). The desired salt of a basic compound may be prepared by methods known to

those of skill in the art by treating the compound with an acid. In some embodiments, inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. In some embodiments, organic acids include, but are not limited to, formic acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, sulfonic acids, and salicylic acid. Salts of basic compounds with amino acids, such as aspartate salts and glutamate salts, can also be prepared. The desired salt of an acidic compound can be prepared by methods known to those of skill in the art by treating the compound with a base. In some embodiments, inorganic salts of acid compounds include, but are not limited to, alkali metal and alkaline earth salts, such as sodium salts, potassium salts, magnesium salts, and calcium salts; ammonium salts; and aluminum salts. In some embodiments, organic salts of acid compounds include, but are not limited to, procaine, dibenzylamine, N-ethylpiperidine, N,N-dibenzylethylenediamine, and triethylamine salts. Salts of acidic compounds with amino acids, such as lysine salts, can also be prepared.

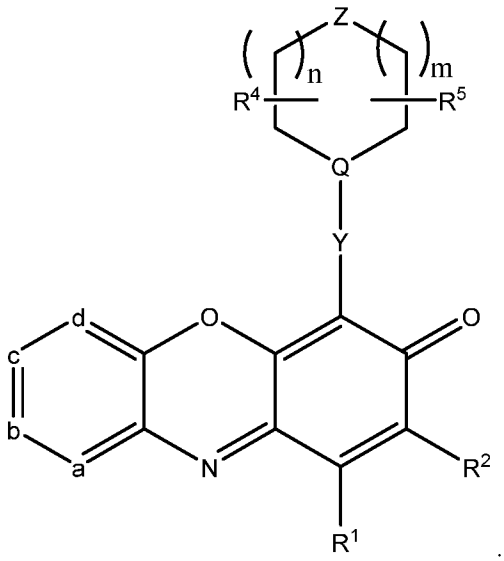
[0076] Included herein, if chemically possible, are all stereoisomers of the compounds, including diastereomers and enantiomers. Also included are mixtures of possible stereoisomers in any ratio, including, but not limited to, racemic mixtures. Unless stereochemistry is explicitly indicated in a structure, the structure is intended to embrace all possible stereoisomers of the compound depicted. If stereochemistry is explicitly indicated for one portion or portions of a molecule, but not for another portion or portions of a molecule, the structure is intended to embrace all possible stereoisomers for the portion or portions where stereochemistry is not explicitly indicated.

[0077] The description of compounds herein also includes all isotopologues, in some embodiments, partially deuterated or perdeuterated analogs of all compounds herein.

[0078] "Reduced form" indicates the form of the compound when a two electron reduction of the oxidized ring is effected. For example, the reduced form of the compounds described herein indicates:



(II), wherein R^1, R^2, R^4, R^5, a, b, c, d, Y, Q, n, m, and Z are defined herein. The "oxidized form" indicates the following form of the compound:



[0079] The term "alkyl" is intended to embrace a saturated linear, branched, or cyclic hydrocarbon, or any combination thereof, unless otherwise specifically indicated. The point of attachment of the alkyl group to the remainder of the molecule can be at any chemically possible location on the alkyl group. In some embodiments, an alkyl has from 1-10 carbon atoms ("C_1-C_{10} alkyl"), from 3-10 carbon atoms ("C_3-C_{10} alkyl"), from 3-8 carbon atoms ("C_3-C_8 alkyl"), from 1 to 6 carbon atoms ("C_1-C_6 alkyl"), from 1 to 4 carbon atoms ("C_1-C_4 alkyl"), from 1 to 3 carbon atoms ("C_1-C_3 alkyl"), or from 1 to 2 carbon atoms ("C_1-C_2 alkyl"). In some embodiments, non-limiting examples of "C_1-C_6 alkyl" include methyl, ethyl,

n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, cyclopropyl-methyl, methyl-cyclopropyl, pentyl, cyclopentyl, hexyl, and cyclohexyl.

[0080] "Cycloalkyl" is a cyclic alkyl group as defined herein. In some embodiments, cycloalkyl has from 3 to 10 carbon ring atoms ("C_3-C_{10} cycloalkyl"). In some embodiments, cycloalkyl has from 3 to 8 carbon ring atoms ("C_3-C_8 cycloalkyl"). In some embodiments, cycloalkyl has from 3 to 6 carbon ring atoms ("C_3-C_6 cycloalkyl").

[0081] A "carbocyclic ring" is a cyclic ring wherein all ring atoms are carbons. The ring may be saturated, or may comprise one or more double or triple bonds between ring atoms. In some embodiments, a carbocyclic ring comprises 3-8 ring atoms ("3-8 membered carbocyclic ring"). In some embodiments, a carbocyclic ring comprises 4-8 ring atoms ("4-8 membered carbocyclic ring").

[0082] "Deuterated form" means the compound is isotopically enriched with deuterium in place of H in at least one atom.

[0083] "DHA" means docosahexaenoic acid.

[0084] The term "haloalkyl" is intended to embrace any alkyl substituent having at least one halogen substituent (e.g. one, two, three, four, or greater than four halogen substituents, provided the number of halogen substituents is chemically possible); the halogen can be attached via any valence on the alkyl group. In some embodiments, a haloalkyl has from 1 to 6 carbon atoms ("C_1-C_6 haloalkyl"), from 1 to 4 carbon atoms ("C_1-C_4 haloalkyl") or from 1 to 2 carbons ("C_1-C_2 haloalkyl"). In some embodiments, C_1-C_6 haloalkyl includes $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CH_2F$, $-CH_2Cl$, $-CF_2CF_3$, 2-trifluoromethylcyclopropyl, and 2-fluoro-cyclopropyl.

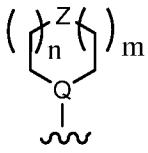
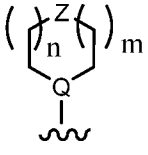
[0085] "Halogen" or "halo" designates fluoro, chloro, bromo, and iodo.

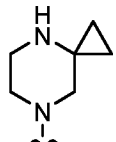
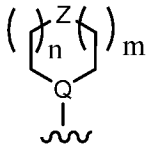
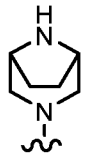
[0086] The term "aryl" is intended to embrace an aromatic cyclic hydrocarbon group of from 6-10 carbon atoms having a single ring (e.g., phenyl) or two fused rings (e.g. naphthyl). In some embodiments, an aryl has from 6-10 carbon ring atoms ("C_6-C_{10} aryl"). In some embodiments, an aryl has 6 carbon ring atoms (e.g. "6-membered aryl").

[0087] The terms "heterocycle", "heterocyclic", "heterocyclo", and "heterocyclyl" are intended to encompass a saturated or partially unsaturated carbocyclic group having one or two (fused, spirocyclic, bridged) rings incorporating one, two, three or four heteroatoms within the ring(s) (chosen from nitrogen, oxygen, and/or sulfur). Both rings may be non-aromatic, or an aromatic ring may be fused with a non-aromatic ring. The attachment point of

the heterocyclic group to the rest of the molecule may be either through a C or N in the ring(s). In some embodiments, non-limiting examples of heterocycles include azetidine, oxetane, morpholine, piperidine, piperazine, thiazolidine, pyrazolidine, pyrazoline, pyrrolidine, tetrahydropyran, tetrahydrofuran, and the like. In some embodiments, a heterocyclic group is saturated (i.e. the bonds between ring atoms are all saturated). In some embodiments, a heterocyclic group comprises one or more unsaturated bonds. In some embodiments, a heterocyclic group comprises 5-15 ring atoms. In some embodiments, a heterocyclic group comprises 3-8 ring atoms ("3-8 membered heterocyclic ring"). In some embodiments, a heterocyclic group comprises 4-8 ring atoms ("4-8 membered heterocyclic ring"). In some embodiments, a heterocyclic group comprises 3-8 ring atoms, and is saturated within the ring atoms ("3-8 membered saturated heterocyclyl").

[0088] A "6-membered heteroaryl" is intended to encompass an aromatic, carbocyclic group having 6 ring atoms, and incorporating one, two, three or four heteroatoms as ring atoms (chosen from nitrogen, oxygen, and/or sulfur). The attachment point of the heteroaryl group to the rest of the molecule may be either through a C or N in the ring(s). In some embodiments, non-limiting examples of 6-membered heteroaryl include pyridine, pyrazine, triazine, pyrimidine, pyridazine, and the like.

[0089] In some embodiments, R^4 and R^5 together with the intervening atom(s) form a 3-8 membered carbocylic or 3-8 membered heterocyclic ring, wherein the 3-8 membered carbocylic or 3-8 membered heterocyclic ring is optionally substituted as defined herein. In such embodiments, such optionally substituted 3-8 membered carbocylic or 3-8 membered heterocyclic ring, together with the remaining atoms in the  ring, form a 5-15 membered fused, bicyclic, or spiro carbocyclic or 5-15 membered fused, bicyclic, or spiro heterocyclic ring. In some embodiments, various examples include, but are not limited to, the following: (1) in some embodiments, R^4 and R^5 form a 3-membered carbocyclic ring, which together with the remaining atoms in the  ring form an 8-membered spiro

heterocyclic ring such as:  ; (2) in some embodiments, R^4 and R^5 form a 5-membered heterocyclic ring  , which together with the remaining atoms in the ring form an 8-membered bicyclic heterocyclic ring such as:  .

[0090] For all embodiments herein in which a particular group is described as being "optionally substituted with one or more substituents", it is to be understood that only chemical possible substitutions are contemplated. In some embodiments, the particular group may be optionally substituted with one substituent. In some embodiments, the particular group may be optionally substituted with one or two substituents. In some embodiments, the particular group may be optionally substituted with one to three substituents. In some embodiments, the particular group may be optionally substituted with one to four substituents. In various embodiments, the particular group is optionally substituted with one, two, three, four, or five substituents.

[0091] "SIRS" means Systemic Inflammatory Response Syndrome.

[0092] By "respiratory chain disorder" is meant a disorder which results in the decreased utilization of oxygen by a mitochondrion, cell, tissue, or individual, due to a defect or disorder in a protein or other component contained in the mitochondrial respiratory chain. By "protein or other component contained in the mitochondrial respiratory chain" is meant the components (including, but not limited to, proteins, tetrapyrroles, and cytochromes) comprising mitochondrial complex I, II, III, IV, and/or V. "Respiratory chain protein" refers to the protein components of those complexes, and "respiratory chain protein disorder" is meant a disorder which results in the decreased utilization of oxygen by a mitochondrion, cell, tissue, or individual, due to a defect or disorder in a protein contained in the mitochondrial respiratory chain.

[0093] The terms "Parkinson's," (also called "Parkinsonism" and "Parkinsonian syndrome") ("PD") is intended to include not only Parkinson's disease but also drug-induced

Parkinsonism and post-encephalitic Parkinsonism. Parkinson's disease is also known as paralysis agitans or shaking palsy. It is characterized by tremor, muscular rigidity and loss of postural reflexes. The disease usually progresses slowly with intervals of 10 to 20 years elapsing before the symptoms cause incapacity. Due to their mimicry of effects of Parkinson's disease, treatment of animals with methamphetamine or MPTP has been used to generate models for Parkinson's disease. These animal models have been used to evaluate the efficacy of various therapies for Parkinson's disease.

[0094] The term "Friedreich's ataxia" is sometimes referred to as hereditary ataxia, familial ataxia, or Friedreich's tabes.

[0095] The term "ataxia" is an aspecific clinical manifestation implying dysfunction of parts of the nervous system that coordinate movement, such as the cerebellum. People with ataxia have problems with coordination because parts of the nervous system that control movement and balance are affected. Ataxia may affect the fingers, hands, arms, legs, body, speech, and eye movements. The word ataxia is often used to describe a symptom of incoordination which can be associated with infections, injuries, other diseases, or degenerative changes in the central nervous system. Ataxia is also used to denote a group of specific degenerative diseases of the nervous system called the hereditary and sporadic ataxias. Ataxias are also often associated with hearing impairments.

[0096] There are three types of ataxia: cerebellar ataxia, including vestibulo-cerebellar dysfunction, spino-cerebellar dysfunction, and cerebro-cerebellar dysfunction; sensory ataxia; and vestibular ataxia. In some embodiments, the diseases which are classifiable into spino-cerebellar ataxia or multiple system atrophy are hereditary olivo-ponto-cerebellar atrophy, hereditary cerebellar cortical atrophy, Friedreich's ataxia, Machado-Joseph diseases, Ramsay Hunt syndrome, hereditary dentatorubral-pallidoluysian atrophy, hereditary spastic paraplegia, Shy-Drager syndrome, cortical cerebellar atrophy, striato-nigral degeneration, Marinesco-Sjogren syndrome, alcoholic cortical cerebellar atrophy, paraneoplastic cerebellar atrophy associated with malignant tumor, toxic cerebellar atrophy caused by toxic substances, Vitamin E deficiency due to mutation of a Tocopherol transfer protein (aTTP) or lipid absorption disorder such as Abetalipoproteinemia, cerebellar atrophy associated with endocrine disturbance and the like.

[0097] In some embodiments, ataxia symptoms are motor ataxia, trunk ataxia, limb ataxia and the like, autonomic disturbance such as orthostatic hypotension, dysuria, hypohidrosis,

sleep apnea, orthostatic syncope and the like, stiffness of lower extremity, ocular nystagmus, oculomotor nerve disorder, pyramidal tract dysfunction, extrapyramidal symptoms (postural adjustment dysfunction, muscular rigidity, akinesia, tremors), dysphagia, lingual atrophy, posterior funiculus symptom, muscle atrophy, muscle weakness, deep hyperreflexia, sensory disturbance, scoliosis, kyphoscoliosis, foot deformities, anarthria, dementia, manic state, decreased motivation for rehabilitation and the like.

[0098] A "liver disorder characterized by one or more inflammation and/or oxidative stress biomarkers" means a disorder in which the liver shows a level of one or more biomarkers that are indicative of inflammation and/or oxidative stress. In some embodiments, the disorder is selected from the group consisting of NAFL, NASH, alcoholic hepatitis, cholestatic liver disease, viral hepatitis, drug-induced liver toxicity, hemochromatosis, Wilson's disease, transplant reperfusion injury, and hepatic insufficiency. In some embodiments, hepatic insufficiency is due to traumatic injury, systemic inflammatory response syndrome (SIRS), sepsis, and/or severe illness.

[0099] A "kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers" means a disorder in which the kidney shows a level of one or more biomarkers that are indicative of inflammation and/or oxidative stress. In some embodiments, the disorder is kidney insufficiency (e.g. due to traumatic injury and/or illness).

[00100] "Biomarkers" as used herein, and unless otherwise specified, refers to measureable biological variables representative of the status of biological function within a subject.

[00101] "Isotopologue" means a compound which differs, *i.e.* in the number of neutrons, in its isotopic composition of at least one atom from the parent molecule having a natural isotopic composition. In some or any embodiments, the compound is isotopically enriched.

[00102] The term "isotopic composition," as used herein, and unless otherwise specified, refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural isotopic composition.

[00103] The term "isotopically enriched," as used herein, and unless otherwise specified, refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

[00104] The terms "medical food" or "clinical food" as used herein, generally refers to an ingestible composition that includes an active ingredient, such as a compound described herein or other composition described herein, in addition to one or more of digestible fats, carbohydrates and proteins. Medical foods or clinical foods may be prescribed and/or administered to a subject to address a specific patient population or condition, such as, in some embodiments, a specific deficiency or deficiency syndrome.

[00105] "NAC" means N-Acetylcysteine.

[00106] "NAFL" or "NAFLD" means Non-Alcoholic Fatty Liver Disease.

[00107] "NASH" means Non-Alcoholic Steatohepatitis.

[00108] "Oxidative stress" means an imbalance between the production of free radicals and the ability of the subject to counteract or detoxify their harmful effects through neutralization by antioxidants. The term "oxidative stress disorder" or "oxidative stress disease" encompass both diseases caused by oxidative stress and diseases aggravated by oxidative stress. The terms "oxidative stress disorder" or "oxidative stress disease" encompass both diseases and disorders where the primary cause of the disease is due to a defect in the respiratory chain or another defect preventing normal utilization of energy in mitochondria, cells, or tissue(s), and also diseases and disorders where the primary cause of the disease is not due to a defect in the respiratory chain or another defect preventing normal utilization of energy in mitochondria, cells, or tissue(s). The former set of diseases can be referred to as "primary oxidative stress disorders," while the latter can be referred to as "secondary oxidative stress disorders." It should be noted that the distinction between "diseases caused by oxidative stress" and "diseases aggravated by oxidative stress" is not absolute; a disease may be both a disease caused by oxidative stress and a disease aggravated by oxidative stress. The boundary between "primary oxidative stress disorder" and a "secondary oxidative stress disorder" is more distinct, provided that there is only one primary cause of a disease or disorder and that primary cause is known.

[00109] Bearing in mind the somewhat fluid boundary between diseases caused by oxidative stress and diseases aggravated by oxidative stress, mitochondrial diseases or disorders and

impaired energy processing diseases and disorders tend to fall into the category of diseases caused by oxidative stress, while neurodegenerative disorders and diseases of aging tend to fall into the category of diseases aggravated by oxidative stress. Mitochondrial diseases or disorders and impaired energy processing diseases and disorders are generally primary oxidative stress disorders, while neurodegenerative disorders and diseases of aging may be primary or secondary oxidative stress disorders.

[00110] A variety of disorders/diseases are believed to be caused or aggravated by oxidative stress affecting normal electron flow in the cells, such as mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases and diseases of aging, and can be treated or suppressed using the compounds and methods disclosed herein.

[00111] In some embodiments, including the foregoing embodiment, oxidative stress disorders include, in some embodiments, mitochondrial disorders (including inherited mitochondrial diseases) such as Alpers Disease, Barth syndrome, Beta-oxidation Defects, Carnitine-Acyl-Carnitine Deficiency, Carnitine Deficiency, Creatine Deficiency Syndromes, Co-Enzyme Q10 Deficiency, Complex I Deficiency, Complex II Deficiency, Complex III Deficiency, Complex IV Deficiency, Complex V Deficiency, COX Deficiency, chronic progressive external ophthalmoplegia (CPEO), CPT I Deficiency, CPT II Deficiency, Friedreich's Ataxia (FA), Glutaric Aciduria Type II, Kearns-Sayre Syndrome (KSS), Lactic Acidosis, Long-Chain Acyl-CoA Dehydrongenase Deficiency (LCAD), LCHAD, Leigh Syndrome, Leigh-like Syndrome, Leber's Hereditary Optic Neuropathy (LHON, also referred to as Leber's Disease, Leber's Optic Atrophy (LOA), or Leber's Optic Neuropathy (LON)), Lethal Infantile Cardiomyopathy (LIC), Luft Disease, Multiple Acyl-CoA Dehydrogenase Deficiency (MAD), Medium-Chain Acyl-CoA Dehydrongenase Deficiency (MCAD), Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS), Myoclonic Epilepsy with Ragged Red Fibers (MERRF), Mitochondrial Recessive Ataxia Syndrome (MIRAS), Mitochondrial Cytopathy, Mitochondrial DNA Depletion, Mitochondrial Encephalopathy, Mitochondrial Myopathy, Myoneurogastointestinal Disorder and Encephalopathy (MNGIE), Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP), Pearson Syndrome, Pyruvate Carboxylase Deficiency, Pyruvate Dehydrogenase Deficiency, POLG Mutations, Respiratory Chain Disorder, Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD), SCHAD, Very Long-Chain Acyl-CoA Dehydrongenase Deficiency (VLCAD); myopathies such as cardiomyopathy and encephalomyopathy; neurodegenerative diseases

such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease); motor neuron diseases; neurological diseases such as epilepsy; diseases associated with aging, particularly diseases for which CoQ10 has been proposed for treatment, such as macular degeneration, diabetes (e.g. Type 2 diabetes mellitus), metabolic syndrome; genetic diseases such as Huntington's Disease (which is also a neurological disease); mood disorders such as schizophrenia and bipolar disorder; pervasive developmental disorders such as autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS); cerebrovascular accidents such as stroke; vision impairments such as those caused by neurodegenerative diseases of the eye such as optic neuropathy, Leber's hereditary optic neuropathy, dominant inherited juvenile optic atrophy, optic neuropathy caused by toxic agents, glaucoma, age-related macular degeneration (both "dry" or non-exudative macular degeneration and "wet" or exudative macular degeneration), Stargardt's macular dystrophy, diabetic retinopathy, diabetic maculopathy, retinopathy of prematurity, or ischemic reperfusion-related retinal injury; disorders caused by energy impairment include diseases due to deprivation, poisoning or toxicity of oxygen, and qualitative or quantitative disruption in the transport of oxygen such as haemoglobinopathies, in some embodiments, thalassemia or sickle cell anemia; other diseases in which mitochondrial dysfunction is implicated such as excitoxic, neuronal injury, such as that associated with seizures, stroke and ischemia; and other disorders including renal tubular acidosis; attention deficit/hyperactivity disorder (ADHD); neurodegenerative disorders resulting in hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally inherited diabetes and deafness (MIDD); chronic fatigue; contrast-induced kidney damage; contrast-induced retinopathy damage; Abetalipoproteinemia; retinitis pigmentosum; Wolfram's disease; Tourette syndrome; cobalamin c defect; methylmalonic aciduria; glioblastoma; Down's syndrome; acute tubular necrosis; muscular dystrophies; leukodystrophies; Progressive Supranuclear Palsy; spinal muscular atrophy; hearing loss (e.g. noise induced hearing loss); traumatic brain injury; Juvenile Huntington's Disease; Multiple Sclerosis; NGLY1; Multisystem atrophy; Adrenoleukodystrophy; and Adrenomyeloneuropathy. It is to be understood that certain specific diseases or disorders may fall within more than one category; in some embodiments, Huntington's Disease is a genetic disease as well as a neurological disease. Furthermore,

certain oxidative stress diseases and disorders may also be considered mitochondrial disorders.

[00112] For some disorders amenable to treatment with compounds and methods disclosed herein, the primary cause of the disorder is due to a defect in the respiratory chain or another defect preventing normal utilization of energy in mitochondria, cells, or tissue(s). In some embodiments, disorders falling in this category include inherited mitochondrial diseases, such as Myoclonic Epilepsy with Ragged Red Fibers (MERRF), Mitochondrial Myopathy, Encephalopathy, Lactacidosis, and Stroke (MELAS), Leber's Hereditary Optic Neuropathy (LHON, also referred to as Leber's Disease, Leber's Optic Atrophy (LOA), or Leber's Optic Neuropathy (LON)), Leigh Syndrome, Leigh-like Syndrome, Kearns-Sayre Syndrome (KSS), and Friedreich's Ataxia (FA). For some disorders amenable to treatment with compounds and methods disclosed herein, the primary cause of the disorder is not due to respiratory chain defects or other defects preventing normal utilization of energy in mitochondria, cells, or tissue(s); in some embodiments, disorders falling in this category include stroke and diabetes. However, these latter disorders are particularly aggravated by energy impairments, and are particularly amenable to treatment with compounds disclosed herein in order to ameliorate the condition. In some embodiments, such disorders include ischemic stroke and hemorrhagic stroke, where the primary cause of the disorder is due to impaired blood supply to the brain. While an ischemic episode caused by a thrombosis or embolism, or a hemorrhagic episode caused by a ruptured blood vessel, is not primarily caused by a defect in the respiratory chain or another metabolic defect preventing normal utilization of energy, oxidative stress plays a role in the ischemic cascade due to oxygen reperfusion injury following hypoxia (this cascade occurs in heart attacks as well as in strokes). Accordingly, treatment with compounds and methods disclosed herein will mitigate the effects of the disease, disorder or condition. Modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers can also prove beneficial in such disorders both as a therapeutic measure and a prophylactic measure. In some embodiments, for a patient scheduled to undergo non-emergency repair of an aneurysm, enhancing energy biomarkers before and during the pre-operative can improve the patient's prognosis should the aneurysm rupture before successful repair.

Assessment of oxidative stress and efficacy of therapy

[00113] The utility of the compounds, compositions, and methods of the present disclosure for treating or suppressing liver or kidney inflammation and/or oxidative stress may be demonstrated both in vitro and in vivo. For example, the ability of cultured cells to form clones (colonies) may be evaluated as a function of liver or kidney inflammation and/or oxidative stress. Cells are either not treated or are treated with a compound or composition of the disclosure at a certain time (in some embodiments, 30 minutes) prior to exposure to factors which may result in inflammation and/or oxidative stress. The degree of retention of ability to form clones after exposure, in comparison to untreated cells, is directly related to the protective effect of the compounds or compositions.

[00114] In vivo, the utility of the compounds, compositions, and methods of the present disclosure for influence on liver and kidney inflammation and/or oxidative stress may be evaluated by mice exposed to conditions commensurate with the manifestation of inflammation and/or oxidative stress of the liver or kidney. Animals, either pre-dosed with a compound or composition disclosed herein, or not dosed (i.e., control animals), are subjected to conditions or materials which can result in inflammation and/or oxidative stress of the liver and/or kidney. In some embodiments, control animals are expected to survive about 12-15 days. The dosed animals response, in comparison to the controls, is directly related to the protective effect of the compound or composition administered. Additionally, blood collection for metabolomics analyses can be conducted at intervals during testing, while tissue sampling can be conducted at testing end point. Evaluation of blood and tissue samples can be compared to untreated control animals for efficacy.

[00115] Several readily measurable clinical markers are used to assess the metabolic state of patients with oxidative stress disorders. These markers can also be used as indicators of the efficacy of a given therapy, as the level of a marker is moved from the pathological value to the healthy value. These clinical markers include, but are not limited to, energy biomarkers such as lactic acid (lactate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; pyruvic acid (pyruvate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; lactate/pyruvate ratios, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized glutathione levels, or reduced/oxidized glutathione ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized cysteine levels, or reduced/oxidized cysteine ratio either in whole blood, plasma,

lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; phosphocreatine levels, NADH (NADH + H^+) or NADPH (NADPH + H^+) levels; NAD or NADP levels; ATP levels; anaerobic threshold; reduced coenzyme Q (CoQred) levels; oxidized coenzyme Q (CoQox) levels; total coenzyme Q (CoQtot) levels; oxidized cytochrome C levels; reduced cytochrome C levels; oxidized cytochrome C/reduced cytochrome C ratio; acetoacetate levels, β-hydroxy butyrate levels, acetoacetate/β-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; levels of reactive oxygen species; and levels of oxygen consumption (VO_2), levels of carbon dioxide output (VCO_2), and respiratory quotient (VCO_2/VO_2). Several of these clinical markers are measured routinely in exercise physiology laboratories, and provide convenient assessments of the metabolic state of a subject. In one embodiment, the level of one or more energy biomarkers in a patient suffering from an oxidative stress disorder, such as Friedreich's ataxia, Leber's hereditary optic neuropathy, MELAS, KSS or CoQ10 deficiency, is improved to within two standard deviations of the average level in a healthy subject. In another embodiment, the level of one or more of these energy biomarkers in a patient suffering from an oxidative stress disorder, such as Friedreich's ataxia, Leber's hereditary optic neuropathy, MELAS, KSS or CoQ10 deficiency is improved to within one standard deviation of the average level in a healthy subject. Exercise intolerance can also be used as an indicator of the efficacy of a given therapy, where an improvement in exercise tolerance (i.e., a decrease in exercise intolerance) indicates efficacy of a given therapy.

[00116] Several metabolic biomarkers have already been used to evaluate efficacy of CoQ10, and these metabolic biomarkers can be monitored as energy biomarkers for use in the methods disclosed herein. Lactate, a product of the anaerobic metabolism of glucose, is removed by reduction to pyruvate in an aerobic setting or by oxidative metabolism, which is dependent on a functional mitochondrial respiratory chain. Dysfunction of the respiratory chain may lead to inadequate removal of lactate and pyruvate from the circulation and elevated lactate/pyruvate ratios are observed in mitochondrial cytopathies (see Scriver CR, The metabolic and molecular bases of inherited disease, 7th ed., New York: McGraw-Hill, Health Professions Division, 1995; and Munnich et al., J. Inherit. Metab. Dis. 15(4):448-55 (1992)). Blood lactate/pyruvate ratio (Chariot et al., Arch. Pathol. Lab. Med. 118(7):695-7 (1994)) is, therefore, widely used as a noninvasive test for detection of mitochondrial cytopathies (see again Scriver CR, The metabolic and molecular bases of inherited disease, 7th ed., New York: McGraw-Hill, Health Professions Division, 1995; and Munnich et al., J.

Inherit. Metab. Dis. 15(4):448-55 (1992)) and toxic mitochondrial myopathies (Chariot et al., Arthritis Rheum. 37(4):583-6 (1994)). Changes in the redox state of liver mitochondria can be investigated by measuring the arterial ketone body ratio (acetoacetate/3-hydroxybutyrate: AKBR) (Ueda et al., J. Cardiol. 29(2):95-102 (1997)). Urinary excretion of 8-hydroxy-2′-deoxyguanosine (8-OHdG) often has been used as a biomarker to assess the extent of repair of ROS-induced DNA damage in both clinical and occupational settings (Erhola et al., FEBS Lett. 409(2):287-91 (1997); Honda et al., Leuk. Res. 24(6):461-8 (2000); Pilger et al., Free Radic. Res. 35(3):273-80 (2001); Kim et al. Environ Health Perspect 112(6):666-71 (2004)).

[00117] Magnetic resonance spectroscopy (MRS) has been useful in the diagnoses of mitochondrial cytopathy by demonstrating elevations in cerebrospinal fluid (CSF) and cortical white matter lactate using proton MRS (1H-MRS) (Kaufmann et al., Neurology 62(8):1297-302 (2004)). Phosphorous MRS (31P-MRS) has been used to demonstrate low levels of cortical phosphocreatine (PCr) (Matthews et al., Ann. Neurol. 29(4):435-8 (1991)), and a delay in PCr recovery kinetics following exercise in skeletal muscle (Matthews et al., Ann. Neurol. 29(4):435-8 (1991); Barbiroli et al., J. Neurol. 242(7):472-7 (1995); Fabrizi et al., J. Neurol. Sci. 137(1):20-7 (1996)). A low skeletal muscle PCr has also been confirmed in patients with mitochondrial cytopathy by direct biochemical measurements.

[00118] Exercise testing is particularly helpful as an evaluation and screening tool in mitochondrial myopathies. One of the hallmark characteristics of mitochondrial myopathies is a reduction in maximal whole body oxygen consumption (VO2max) (Taivassalo et al., Brain 126(Pt 2):413-23 (2003)). Given that VO2max is determined by cardiac output (Qc) and peripheral oxygen extraction (arterial-venous total oxygen content) difference, some mitochondrial cytopathies affect cardiac function where delivery can be altered; however, most mitochondrial myopathies show a characteristic deficit in peripheral oxygen extraction (A-V O2 difference) and an enhanced oxygen delivery (hyperkinetic circulation) (Taivassalo et al., Brain 126(Pt 2):413-23 (2003)). This can be demonstrated by a lack of exercise induced deoxygenation of venous blood with direct AV balance measurements (Taivassalo et al., Ann. Neurol. 51(1):38-44 (2002)) and non-invasively by near infrared spectroscopy (Lynch et al., Muscle Nerve 25(5):664-73 (2002); van Beekvelt et al., Ann. Neurol. 46(4):667-70 (1999)).

[00119] Several of these energy biomarkers are discussed in more detail as follows. It should be emphasized that, while certain energy biomarkers are discussed and enumerated herein,

the embodiments are not limited to modulation, normalization or enhancement of only these enumerated energy biomarkers.

[00120] Lactic acid (lactate) levels: Mitochondrial dysfunction typically results in abnormal levels of lactic acid, as pyruvate levels increase and pyruvate is converted to lactate to maintain capacity for glycolysis. Mitochondrial dysfunction can also result in abnormal levels of NADH + H^+, NADPH + H^+, NAD, or NADP, as the reduced nicotinamide adenine dinucleotides are not efficiently processed by the respiratory chain. Lactate levels can be measured by taking samples of appropriate bodily fluids such as whole blood, plasma, or cerebrospinal fluid. Using magnetic resonance, lactate levels can be measured in virtually any volume of the body desired, such as the brain.

[00121] Measurement of cerebral lactic acidosis using magnetic resonance in MELAS patients is described in Kaufmann et al., Neurology 62(8):1297 (2004). Values of the levels of lactic acid in the lateral ventricles of the brain are presented for two mutations resulting in MELAS, A3243G and A8344G. Whole blood, plasma, and cerebrospinal fluid lactate levels can be measured by commercially available equipment such as the YSI 2300 STAT Plus Glucose & Lactate Analyzer (YSI Life Sciences, Ohio).

[00122] NAD, NADP, NADH and NADPH levels: Measurement of NAD, NADP, NADH (NADH + H^+) or NADPH (NADPH + H^+) can be measured by a variety of fluorescent, enzymatic, or electrochemical techniques, e.g., the electrochemical assay described in US 2005/0067303.

[00123] GSH, GSSG, Cys, and CySS levels: Briefly, plasma levels of GSH, GSSG, Cys, and CySS are used to calculate the in vivo E_h values. Samples are collected using the procedure of Jones et al (2009 Free Radical Biology & Medicine 47(10) pp. 1329-1338), and bromobimane is used to alkylate free thiols and HPLC and either electrochemical or MSMS to separate, detect, and quantify the molecules. As described in more detail in US 2015-0216820 filed September 6, 2013, we have developed a method for different experimental parameters to analyze the most common monothiols and disulfide (cystine, cysteine, reduced (GSH) and oxidized glutathione (GSSG)) present in human plasma, and using Bathophenanthroline disulfonic acid as the internal standard (IS). Complete separation of all the targets analytes and IS at 35 °C on a C18 RP column (250 mm×4.6mm, 3 micron) was achieved using 0.2% TFA:Acetonitrile as a mobile phase pumped at the rate of 0.6 ml min−1 using electrochemical detector in DC mode at the detector potential of 1475 mV.

[00124] Oxygen consumption (vO_2 or VO_2), carbon dioxide output (vCO_2 or VCO_2), and respiratory quotient (VCO_2/VO_2): vO_2 is usually measured either while resting (resting vO_2) or at maximal exercise intensity (vO_2 max). Optimally, both values will be measured. However, for severely disabled patients, measurement of vO_2 max may be impractical. Measurement of both forms of vO_2 is readily accomplished using standard equipment from a variety of vendors, e.g. Korr Medical Technologies, Inc. (Salt Lake City, Utah). VCO_2 can also be readily measured, and the ratio of VCO_2 to VO_2 under the same conditions (VCO_2/VO_2, either resting or at maximal exercise intensity) provides the respiratory quotient (RQ).

[00125] Oxidized Cytochrome C, reduced Cytochrome C, and ratio of oxidized Cytochrome C to reduced Cytochrome C: Cytochrome C parameters, such as oxidized cytochrome C levels (Cyt Cox), reduced cytochrome C levels (Cyt Cred), and the ratio of oxidized cytochrome C/reduced cytochrome C ratio (Cyt Cox)/(Cyt Cred), can be measured by in vivo near infrared spectroscopy. See, e.g., Rolfe, P., "In vivo near-infrared spectroscopy," Annu. Rev. Biomed. Eng. 2:715-54 (2000) and Strangman et al., "Non-invasive neuroimaging using near-infrared light" Biol. Psychiatry 52:679-93 (2002).

[00126] Exercise tolerance/Exercise intolerance: Exercise intolerance is defined as "the reduced ability to perform activities that involve dynamic movement of large skeletal muscles because of symptoms of dyspnea or fatigue" (Piña et al., Circulation 107:1210 (2003)). Exercise intolerance is often accompanied by myoglobinuria, due to breakdown of muscle tissue and subsequent excretion of muscle myoglobin in the urine. Various measures of exercise intolerance can be used, such as time spent walking or running on a treadmill before exhaustion, time spent on an exercise bicycle (stationary bicycle) before exhaustion, and the like. Treatment with the compounds or methods disclosed herein can result in about a 10% or greater improvement in exercise tolerance (in some embodiments, about a 10% or greater increase in time to exhaustion, in some embodiments, from 10 minutes to 11 minutes), about a 20% or greater improvement in exercise tolerance, about a 30% or greater improvement in exercise tolerance, about a 40% or greater improvement in exercise tolerance, about a 50% or greater improvement in exercise tolerance, about a 75% or greater improvement in exercise tolerance, or about a 100% or greater improvement in exercise tolerance. While exercise tolerance is not, strictly speaking, an energy biomarker, for the purposes disclosed herein,

modulation, normalization, or enhancement of energy biomarkers includes modulation, normalization, or enhancement of exercise tolerance.

[00127] Similarly, tests for normal and abnormal values of pyruvic acid (pyruvate) levels, lactate/pyruvate ratio, ATP levels, anaerobic threshold, reduced coenzyme Q (CoQred) levels, oxidized coenzyme Q (CoQox) levels, total coenzyme Q (CoQtot) levels, oxidized cytochrome C levels, reduced cytochrome C levels, oxidized cytochrome C/reduced cytochrome C ratio, GSH and cysteine reduced, oxidized, total levels and ratio, acetoacetate levels, β-hydroxy butyrate levels, acetoacetate/β-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels, and levels of reactive oxygen species are known in the art and can be used to evaluate efficacy of the compounds and methods disclosed herein. (For the purposes disclosed herein, modulation, normalization, or enhancement of energy biomarkers includes modulation, normalization, or enhancement of anaerobic threshold.)

[00128] Table 1, following, illustrates the effect that various dysfunctions can have on biochemistry and energy biomarkers. It also indicates the physical effect (such as a disease symptom or other effect of the dysfunction) typically associated with a given dysfunction. It should be noted that any of the energy biomarkers listed in the table, in addition to energy biomarkers enumerated elsewhere, can also be modulated, enhanced, or normalized by the compounds and methods disclosed herein. RQ = respiratory quotient; BMR = basal metabolic rate; HR (CO) = heart rate (cardiac output); T = body temperature (preferably measured as core temperature); AT = anaerobic threshold; pH = blood pH (venous and/or arterial).

Table 1

Site of Dysfunction	Biochemical Event	Measurable Energy Biomarker	Physical Effect
Respiratory Chain	↑ NADH	Δ lactate, Δ lactate: pyruvate ratio; and Δ acetoacetate: β-hydroxy butyrate ratio	Metabolic dyscrasia & fatigue
Respiratory Chain	↓ H^+ gradient	Δ ATP	Organ dependent dysfunction
Respiratory Chain	↓ Electron flux	Δ VO2, RQ, BMR, ΔT, AT, pH	Metabolic dyscrasia & fatigue
Mitochondria & cytosol	↓ ATP, ↓ VO_2	Δ Work, ΔHR (CO)	Exercise intolerance
Mitochondria & cytosol	↓ ATP	Δ PCr	Exercise intolerance

Site of Dysfunction	Biochemical Event	Measurable Energy Biomarker	Physical Effect
Respiratory Chain	↓ Cyt COx/Red	Δ λ ~700 – 900 nm (Near Infrared Spectroscopy)	Exercise intolerance
Intermediary metabolism	↓ Catabolism	Δ C14-Labeled substrates	Metabolic dyscrasia & fatigue
Respiratory Chain	↓ Electron flux	Δ Mixed Venous VO_2	Metabolic dyscrasia & fatigue
Mitochondria & cytosol	↑ Oxidative stress	Δ Tocopherol & Tocotrienols, CoQ10, docosahexaenoic acid	Uncertain
Mitochondria & cytosol	↑ Oxidative stress	Δ $Glutathione_{red}$	Uncertain
Mitochondria & cytosol	Nucleic acid oxidation	Δ 8-hydroxy 2-deoxy guanosine	Uncertain
Mitochondria & cytosol	Lipid oxidation	Δ Isoprostane(s), eicosanoids	Uncertain
Cell membranes	Lipid oxidation	Δ Ethane (breath)	Uncertain
Cell membranes	Lipid oxidation	Δ Malondialdehyde	Uncertain

[00129] Treatment of a subject afflicted by an oxidative stress disorder in accordance with the methods disclosed herein may result in the inducement of a reduction or alleviation of symptoms in the subject, e.g., to halt the further progression of the disorder.

[00130] Partial or complete suppression of the oxidative stress disorder can result in a lessening of the severity of one or more of the symptoms that the subject would otherwise experience. In some embodiments, partial suppression of MELAS could result in reduction in the number of stroke-like or seizure episodes suffered.

[00131] Any one or any combination of the energy biomarkers described herein provide conveniently measurable benchmarks by which to gauge the effectiveness of treatment or suppressive therapy. Additionally, other energy biomarkers are known to those skilled in the art and can be monitored to evaluate the efficacy of treatment or suppressive therapy.

Use of compounds for modulation of energy biomarkers

[00132] In addition to monitoring energy biomarkers to assess the status of treatment or suppression of oxidative stress disorders, the compounds disclosed herein can be used in subjects or patients to modulate one or more energy biomarkers. Modulation of energy biomarkers can be done to normalize energy biomarkers in a subject, or to enhance energy biomarkers in a subject.

[00133] Normalization of one or more energy biomarkers is defined as either restoring the level of one or more such energy biomarkers to normal or near-normal levels in a subject whose levels of one or more energy biomarkers show pathological differences from normal levels (i.e., levels in a healthy subject), or to change the levels of one or more energy biomarkers to alleviate pathological symptoms in a subject. Depending on the nature of the energy biomarker, such levels may show measured values either above or below a normal value. In some embodiments, a pathological lactate level is typically higher than the lactate level in a normal (i.e., healthy) person, and a decrease in the level may be desirable. A pathological ATP level is typically lower than the ATP level in a normal (i.e., healthy) person, and an increase in the level of ATP may be desirable. Accordingly, normalization of energy biomarkers can involve restoring the level of energy biomarkers to within about at least two standard deviations of normal in a subject, more preferably to within about at least one standard deviation of normal in a subject, to within about at least one-half standard deviation of normal, or to within about at least one-quarter standard deviation of normal.

[00134] Enhancement of the level of one or more energy biomarkers is defined as changing the extant levels of one or more energy biomarkers in a subject to a level which provides beneficial or desired effects for the subject. In some embodiments, a person undergoing strenuous effort or prolonged vigorous physical activity, such as mountain climbing, could benefit from increased ATP levels or decreased lactate levels. As described herein, normalization of energy biomarkers may not achieve the optimum state for a subject with an oxidative stress disease, and such subjects can also benefit from enhancement of energy biomarkers. In some embodiments, subjects who could benefit from enhanced levels of one or more energy biomarkers include, but are not limited to, subjects undergoing strenuous or prolonged physical activity, subjects with chronic energy problems, or subjects with chronic respiratory problems. Such subjects include, but are not limited to, pregnant females, particularly pregnant females in labor; neonates, particularly premature neonates; subjects exposed to extreme environments, such as hot environments (temperatures routinely exceeding about 85-86 degrees Fahrenheit or about 30 degrees Celsius for about 4 hours daily or more), cold environments (temperatures routinely below about 32 degrees Fahrenheit or about 0 degrees Celsius for about 4 hours daily or more), or environments with lower-than-average oxygen content, higher-than-average carbon dioxide content, or higher-than-average levels of air pollution (airline travelers, flight attendants, subjects at elevated altitudes,

subjects living in cities with lower-than-average air quality, subjects working in enclosed environments where air quality is degraded); subjects with lung diseases or lower-than-average lung capacity, such as tubercular patients, emphysema patients, and cystic fibrosis patients; subjects recovering from surgery or illness; elderly subjects, including elderly subjects experiencing decreased energy; subjects suffering from chronic fatigue, including chronic fatigue syndrome; subjects undergoing acute trauma; subjects in shock; subjects requiring acute oxygen administration; subjects requiring chronic oxygen administration; or other subjects with acute, chronic, or ongoing energy demands who can benefit from enhancement of energy biomarkers.

[00135] Accordingly, when an increase in a level of one or more energy biomarkers is beneficial to a subject, enhancement of the one or more energy biomarkers can involve increasing the level of the respective energy biomarker or energy biomarkers to about at least one-quarter standard deviation above normal, about at least one-half standard deviation above normal, about at least one standard deviation above normal, or about at least two standard deviations above normal. Alternatively, the level of the one or more energy biomarkers can be increased by about at least 10% above the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 20% above the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 30% above the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 40% above the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 50% above the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 75% above the subject's level of the respective one or more energy biomarkers before enhancement, or by about at least 100% above the subject's level of the respective one or more energy biomarkers before enhancement.

[00136] When a decrease in a level of one or more energy biomarkers is desired to enhance one or more energy biomarkers, the level of the one or more energy biomarkers can be decreased by an amount of about at least one-quarter standard deviation of normal in a subject, decreased by about at least one-half standard deviation of normal in a subject, decreased by about at least one standard deviation of normal in a subject, or decreased by about at least two standard deviations of normal in a subject. Alternatively, the level of the one or more energy biomarkers can be decreased by about at least 10% below the subject's

level of the respective one or more energy biomarkers before enhancement, by about at least 20% below the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 30% below the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 40% below the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 50% below the subject's level of the respective one or more energy biomarkers before enhancement, by about at least 75% below the subject's level of the respective one or more energy biomarkers before enhancement, or by about at least 90% below the subject's level of the respective one or more energy biomarkers before enhancement.

Use of compounds in research applications, experimental systems, and assays

[00137] The compounds disclosed herein can also be used in research applications. They can be used in in vitro, in vivo, or ex vivo experiments to modulate one or more energy biomarkers in an experimental system. Such experimental systems can be cell samples, tissue samples, cell components or mixtures of cell components, partial organs, whole organs, or organisms. Any one or more of the compounds as described herein can be used in experimental systems or research applications. Such research applications can include, but are not limited to, use as assay reagents, elucidation of biochemical pathways, or evaluation of the effects of other agents on the metabolic state of the experimental system in the presence/absence of one or more compounds disclosed herein.

[00138] Additionally, the compounds disclosed herein can be used in biochemical tests or assays. Such tests can include incubation of one or more compounds disclosed herein with a tissue or cell sample from a subject to evaluate a subject's potential response (or the response of a specific subset of subjects) to administration of said one or more compounds, or to determine which compound disclosed herein produces the optimum effect in a specific subject or subset of subjects. One such test or assay would involve 1) obtaining a cell sample or tissue sample from a subject in which modulation of one or more energy biomarkers can be assayed; 2) administering one or more compounds disclosed herein to the cell sample or tissue sample; and 3) determining the amount of modulation of the one or more energy biomarkers after administration of the one or more compounds, compared to the status of the energy biomarker prior to administration of the one or more compounds. Another such test or assay would involve 1) obtaining a cell sample or tissue sample from a subject in which

modulation of one or more energy biomarkers can be assayed; 2) administering at least two compounds disclosed herein to the cell sample or tissue sample; 3) determining the amount of modulation of the one or more energy biomarkers after administration of the at least two compounds, compared to the status of the energy biomarker prior to administration of the at least two compounds, and 4) selecting a compound or compounds for use in treatment, suppression, or modulation based on the amount of modulation determined in step 3.

Pharmaceutical compositions

[00139] The terms "pharmaceutical formulation" and "pharmaceutical composition" are used interchangeably herein.

[00140] The term "pharmaceutically acceptable," as used herein, generally refers to those properties and/or substances that are acceptable to the patient from a pharmacological/ toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance, and bioavailability.

[00141] The compounds described herein can be formulated as pharmaceutical compositions by formulation with additives such as pharmaceutically acceptable excipients, pharmaceutically acceptable carriers, and pharmaceutically acceptable vehicles. The terms "pharmaceutically acceptable excipients," "pharmaceutically acceptable carriers," and "pharmaceutically acceptable vehicles" are used interchangeably herein. Suitable pharmaceutically acceptable excipients, carriers and vehicles include processing agents and drug delivery modifiers and enhancers, such as, in some embodiments, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), and "Remington: The Science and Practice of Pharmacy," Lippincott Williams & Wilkins, Philadelphia, 20th edition (2003) and 21st edition (2005), incorporated herein by reference.

[00142] A pharmaceutical composition can comprise a unit dose formulation, where the unit dose is a dose sufficient to have a therapeutic, prophylactic, or suppressive effect or an

amount effective to modulate, normalize, or enhance an energy biomarker. The unit dose may be sufficient as a single dose to have a therapeutic, prophylactic, or suppressive effect or an amount effective to modulate, normalize, or enhance an energy biomarker. Alternatively, the unit dose may be a dose administered periodically in a course of treatment, prophylaxis, or suppression of a disorder, or to modulate, normalize, or enhance an energy biomarker.

[00143] Pharmaceutical compositions containing the compounds disclosed herein may be in any form suitable for the intended method of administration, including, in some embodiments, a solution, a suspension, or an emulsion. Liquid carriers are typically used in preparing solutions, suspensions, and emulsions. Liquid carriers contemplated for use in the practice include in some embodiments, water, saline, pharmaceutically acceptable organic solvent(s), pharmaceutically acceptable oils or fats, and the like, as well as mixtures of two or more thereof. The liquid carrier may contain other suitable pharmaceutically acceptable additives such as solubilizers, emulsifiers, nutrients, buffers, preservatives, suspending agents, thickening agents, viscosity regulators, stabilizers, and the like. Suitable organic solvents include, in some embodiments, monohydric alcohols, such as ethanol, and polyhydric alcohols, such as glycols. Suitable oils include, in some embodiments, soybean oil, coconut oil, olive oil, safflower oil, cottonseed oil, and the like. For parenteral administration, the carrier can also be an oily ester such as ethyl oleate, isopropyl myristate, and the like. Compositions disclosed herein may also be in the form of microparticles, microcapsules, liposomal encapsulates, and the like, as well as combinations of any two or more thereof.

[00144] Time-release or controlled release delivery systems may be used, such as a diffusion controlled matrix system or an erodible system, as described for example in: Lee, "Diffusion-Controlled Matrix Systems", pp. 155-198 and Ron and Langer, "Erodible Systems", pp. 199-224, in "Treatise on Controlled Drug Delivery", A. Kydonieus Ed., Marcel Dekker, Inc., New York 1992. The matrix may be, in some embodiments, a biodegradable material that can degrade spontaneously in situ and in vivo, in some embodiments, by hydrolysis or enzymatic cleavage, e.g., by proteases. The delivery system may be, in some embodiments, a naturally occurring or synthetic polymer or copolymer, in some embodiments, in the form of a hydrogel. Exemplary polymers with cleavable linkages include polyesters, polyorthoesters, polyanhydrides, polysaccharides, poly(phosphoesters), polyamides, polyurethanes, poly(imidocarbonates) and poly(phosphazenes).

[00145] The compounds described above may, in some embodiments, be incorporated in a broader formulation or composition, e.g., formulated with other components, to provide for different applications and to serve different purposes, such as to improve bioavailability, improve storage, controlled release, solubility, mode of administration, and the like. In some embodiments, non-limiting examples of such compositions include medical foods and pharmaceutical formulations. The compositions may be formulated for internal or topical use.

[00146] In some cases, the compositions described herein may be co-administered, including as co-formulations, with other compositions comprising a therapeutic agent. In some embodiments, such other compositions are used in the treatment of certain disorders or conditions, in applications where such compositions have demonstrated efficacy, in order to improve that efficacy and/or reduce adverse side effects or reactions. In some embodiments, the compositions described herein may be co-administered with one or more omega-3 fatty acids (also referred to as n-3 polyunsaturated fatty acids or n-3 PUFA), such as docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA), as well as CoQ10 and n-acetyl cysteine (NAC) in conditions that are typically treated using such compositions. Such co-administration may be employed, in some embodiments, in the treatment of liver disorders, e.g., non-alcoholic fatty liver disease (NAFLD), pediatric NAFLD, and diseases related to aging. Likewise, such co-administration may be used in cases where such n3-PUFAs are administered to enhance effectiveness of a given treatment, such as in chemotherapy. In addition, co-administration with antivirals, in some embodiments, antivirals for hepatitis, and co-administration in conjunction with standard treatments for Wilson's disease and hemochromatosis to improve effectiveness.

[00147] The compounds disclosed herein may be administered enterally, orally, parenterally, sublingually, by inhalation (e.g. as mists or sprays), rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. In some embodiments, suitable modes of administration include oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intra-arterial, intramuscular, intraperitoneal, intranasal (e.g. via nasal mucosa), subdural, rectal, gastrointestinal, and the like, and directly to a specific or affected organ or tissue. For delivery to the central nervous system, spinal and epidural administration, or administration to cerebral ventricles, can be used. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term

parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intra-sternal injection, or infusion techniques. The compounds are mixed with pharmaceutically acceptable carriers, adjuvants, and vehicles appropriate for the desired route of administration. Oral administration is a preferred route of administration, and formulations suitable for oral administration are preferred formulations. The compounds described for use herein can be administered in solid form, in liquid form, in aerosol form, or in the form of tablets, pills, powder mixtures, capsules, granules, injectables, creams, solutions, suppositories, enemas, colonic irrigations, emulsions, dispersions, food premixes, and in other suitable forms. The compounds can also be administered in liposome formulations. The compounds can also be administered as prodrugs, where the prodrug undergoes transformation in the treated subject to a form which is therapeutically or prophylactically effective. Additional methods of administration are known in the art.

[00148] In some embodiments, especially those embodiments where a formulation is used for injection or other parenteral administration including the routes listed herein, but also including embodiments used for oral, gastric, gastrointestinal, or enteric administration, the formulations and preparations used in the methods disclosed herein are sterile. Sterile pharmaceutical compositions are compounded or manufactured according to pharmaceutical-grade sterilization standards (United States Pharmacopeia Chapters 797, 1072, and 1211; California Business & Professions Code 4127.7; 16 California Code of Regulations 1751, 21 Code of Federal Regulations 211) known to those of skill in the art.

[00149] Injectable preparations, in some embodiments, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, in some embodiments, as a solution in propylene glycol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00150] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed

with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[00151] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

[00152] The compounds disclosed herein can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound disclosed herein, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.W., p. 33 et seq (1976).

[00153] In one composition, the compound is formulated as an admixture with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil and administered orally (PO), intraperitoneal (IP), or subcutaneous (SC). In another composition the compound is formulated as an admixture with propylene glycol and administered PO, IP, or SC.

[00154] In another composition, the compound is adsorbed by admixture to a solid matrix from the group of calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, micro cellulose, and talcum. In some embodiments the adsorbed solid is milled into a free flowing powder and filled into hard gelatin capsules and administered orally.

[00155] In another composition, the compound is admixed with edible oil or propylene glycol and filled into soft gelatin capsules and administered orally.

[00156] In another composition, the compound is admixed with petroleum jelly or dissolved in dimethylsulfoxide and administered topically.

[00157] In another composition, the compound is vaporized in a device such as an e-cigarette and inhaled.

[00158] In another composition, the compound is emulsified as an oil in water solution. In some embodiments the emulsifier is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide and administered topically or orally.

[00159] Also provided are articles of manufacture and kits containing materials useful for treating or suppressing oxidative stress disorders. Also provided are kits comprising any one or more of the compounds as described herein. In some embodiments, the kit disclosed herein comprises the container described herein.

[00160] In other aspects, the kits may be used for any of the methods described herein, including, to treat an individual with a mitochondrial disorder, or to suppress a mitochondrial disorder in an individual.

Medical Foods

[00161] Medical foods are foods that are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone. Such medical foods are labeled for the dietary management of a specific medical disorder, disease or condition for which there are distinctive nutritional requirements, and are intended to be used under medical supervision. In some embodiments, the compositions described herein may be formulated as a medical food, including one or more of dietary carbohydrates, e.g., sugars and starches, dietary fats, dietary proteins, e.g., whey proteins, soy proteins and the like, vitamins, mineral, etc. In some embodiments, the medical food is a nutritionally complete formula. In some embodiments, the medical food is a nutritionally incomplete formula. The compounds described herein may be present in the medical food in any of the amounts or weight percentages described herein; an appropriate amount of the compounds described herein for the particular disease may be determined by one skilled in the art.

Dosing

[00162] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host to which the active ingredient is administered and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, body area, body mass index (BMI), general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the type, progression, and severity of the particular disease undergoing therapy. The pharmaceutical unit dosage chosen is usually fabricated and administered to provide a defined final concentration of drug in the blood, tissues, organs, or other targeted region of the body. The therapeutically effective amount or prophylactically effective amount or effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[00163] In some embodiments, dosages which can be used are a therapeutically effective amount, prophylactically effective amount, or effective amount within the dosage range of about 0.1 mg/kg to about 300 mg/kg body weight, or within about 1.0 mg/kg to about 100 mg/kg body weight, or within about 1.0 mg/kg to about 50 mg/kg body weight, or within about 1.0 mg/kg to about 30 mg/kg body weight, or within about 1.0 mg/kg to about 10 mg/kg body weight, or within about 10 mg/kg to about 100 mg/kg body weight, or within about 50 mg/kg to about 150 mg/kg body weight, or within about 100 mg/kg to about 200 mg/kg body weight, or within about 150 mg/kg to about 250 mg/kg body weight, or within about 200 mg/kg to about 300 mg/kg body weight, or within about 250 mg/kg to about 300 mg/kg body weight. Compounds disclosed herein may be administered in a single daily dose, or the total daily dosage may be administered in divided dosage of two, three or four times daily.

[00164] Single or multiple doses can be administered. In some embodiments, the dose is administered once, twice, three times, four times, five times, or six times. In some embodiments, the dose is administered once per day, twice per day, three times per day, or four times per day. In some embodiments, the dose is administered every hour, every two hours, every three hours, every four hours, every 6 hours, every 12 hours, or every 24 hours.

[00165] Single or multiple doses can be administered prior to or after indications of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered once, twice, three times, four times, five times, or six times during or after appearance of biomarkers of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered once per day, twice per day, three times per day, or four times per day during or after appearance of biomarkers of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered every hour, every two hours, every three hours, every four hours, every 6 hours, every 12 hours, or every 24 hours during or after appearance of biomarkers of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver).

[00166] Single or multiple doses can be administered before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered once, twice, three times, four times, five times, or six times before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered once per day, twice per day, three times per day, or four times per day before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered every hour, every two hours, every three hours, every four hours, every 6 hours, every 12 hours, or every 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered about 30 minutes before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 1 hour before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 2 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 3 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in

the liver), about 4 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 6 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 8 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 10 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), about 12 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver), and/or about 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered about 4 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered about 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver). In some embodiments, the dose is administered about 4 hours and about 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver).

[00167] The one or more inflammation and/or oxidative stress protective agents can be administered about 0 to about 48 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 24 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 12 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 4 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to

about 1 hour after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more protective agent can be administered about 0 to about 30 minutes after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more protective agent can be administered about 0 to about 15 minutes after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 10 minutes after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 5 minutes after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 48 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 24 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 12 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 4 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 2 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 1 hour after appearance of

inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 48 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 24 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 12 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 4 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 2 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 1 hour after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, bout 16 hours, about 17 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 30 hours, about 36 hours, about 42 hours, and/or about 48 hours after appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver).

[00168] The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 48 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver)

in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 12 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 4 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 1 hour before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 30 minutes before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 15 minutes before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 10 minutes before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 0 to about 5 minutes before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 48 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 24 hours before appearance of inflammation and/or oxidative stress (where, in some

embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 12 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 4 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 2 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes to about 1 hour before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 48 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 24 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 12 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 4 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 2 hours before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 30 minutes to about 1 hour

before appearance of inflammation and/or oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) in single or multiple doses. The one or more inflammation and/or oxidative stress protective agent can be administered about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, bout 16 hours, about 17 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 30 hours, about 36 hours, about 42 hours, and/or about 48 hours before appearance of inflammation and/or oxidative stress.

Combinations

[00169] While the compounds disclosed herein can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment or suppression of disorders. In some embodiments, the compound(s) of the disclosure are administered as the sole active pharmaceutical agent that is present in a therapeutically effective or a prophylactically effective amount. Representative agents useful in combination with the compounds disclosed herein for the treatment or suppression of oxidative stress (where, in some embodiments, the inflammation and/or oxidative stress is in the liver) disorders include, but are not limited to, Coenzyme Q, vitamin E, idebenone, MitoQ, vitamins, NAC, and antioxidant compounds. In some embodiments, including any of the foregoing embodiments, an additional agent is co-administered with the compound, wherein the additional agent is selected from the group consisting of omega-3 fatty acids (also referred to as n-3 polyunsaturated fatty acids or n-3 PUFA), such as docosahexaenoic acid DHA) and/or eicosapentaenoic acid (EPA), as well as CoQ10 and n-acetyl cysteine (NAC). In some embodiments, including any of the foregoing embodiments, the co-administered additional agent has a weight % concentration of 1-99% based on the total weight of the compound and the co-administered agent.

[00170] When additional active agents are used in combination with the compounds disclosed herein, the additional active agents may generally be employed in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 53rd Edition (1999), or such therapeutically or prophylactically useful amounts as would be known to one of ordinary skill in the art.

[00171] The compounds disclosed herein and the other therapeutically active agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions disclosed herein may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. When administered in combination with other therapeutic agents, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

Preparation of Compounds

[00172] In general, the nomenclature used in this Application was generated with the help of naming package within the ChemOffice®. version 11.0 suite of programs by CambridgeSoft Corp (Cambridge, Mass.).

[00173] The compounds disclosed herein can be prepared from readily available starting materials; non-limiting exemplary methods are described in the Examples. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Synthetic Reaction Parameters

[00174] The terms "solvent", "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith. Solvents employed in synthesis of the compounds disclosed herein include, in some embodiments, methanol ("MeOH"), acetone, water, acetonitrile, 1,4-dioxane, dimethylformamide ("DMF"), benzene, toluene, xylene, tetrahydrofuran ("THF"), chloroform, methylene chloride (or dichloromethane, ("DCM")), diethyl ether, pyridine and the like, as well as mixtures thereof. Unless specified to the contrary, the solvents used in the reactions disclosed herein are inert organic solvents.

[00175] The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

[00176] The compounds herein are synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing the compounds herein are both readily apparent and accessible to those of skill in the relevant art in light of the teachings described herein. While the Examples illustrate certain of the diverse methods available for use in assembling the compounds herein, they are not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds herein. Synthetic methods for other compounds disclosed herein will be apparent to one skilled in the art in view of the illustrative examples.

[00177] For all of the compounds and methods described herein, the oxidized form can also be used in its reduced form when desired. Likewise, the reduced form can also be used in its oxidized form when desired. The reduced form may readily be converted to the oxidized form using methods known in the art. See e.g. air, silica Miller et al PCT Intl Appl 2006130775 7 Dec 2006. The oxidized form may readily be converted to the reduced form using methods known in the art. See, e.g. Zn, AcOH Fuchs et al EJOC 6 (2009) 833-40.

Exemplary Synthetic Schemes for Preparation of Compounds Disclosed Herein

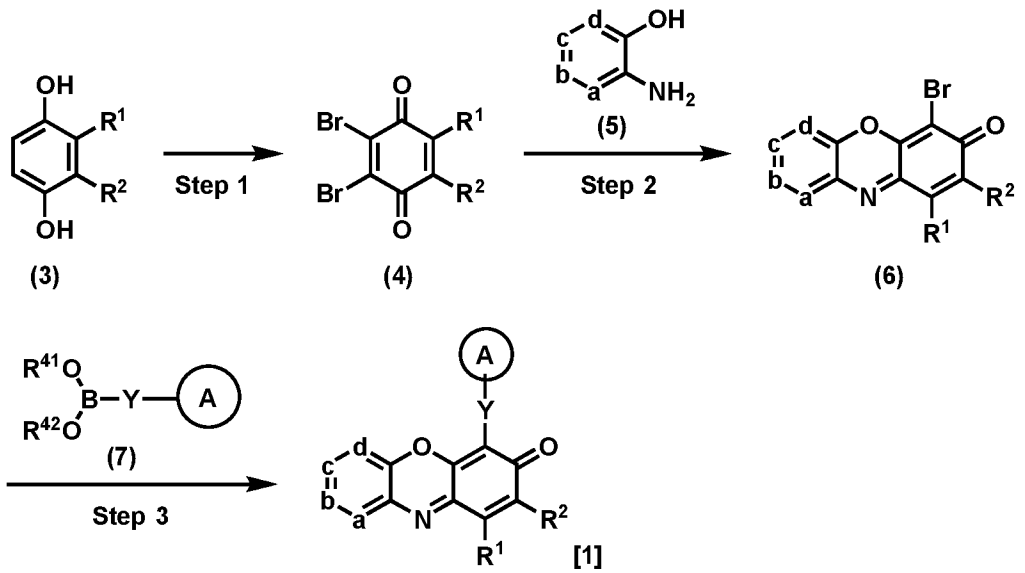
[00178] Hereinbelow, methods of producing compounds described herein are illustrated with examples. However, the scope of the present invention is certainly not limited thereto. These reactions are merely illustrations. The compounds described herein can be produced by appropriately combining known raw material compounds and conventional methods or production methods in accordance therewith based on knowledge of those skilled in the art of synthetic organic chemistry. If a raw material compound to be used is commercially available, such a commercially available compound also can be used.

[00179] A compound represented by Formula I is produced, in some embodiments, by the following production methods. It should be noted that a compound used in the following production methods may form a salt thereof as long as it does not interfere with a reaction.

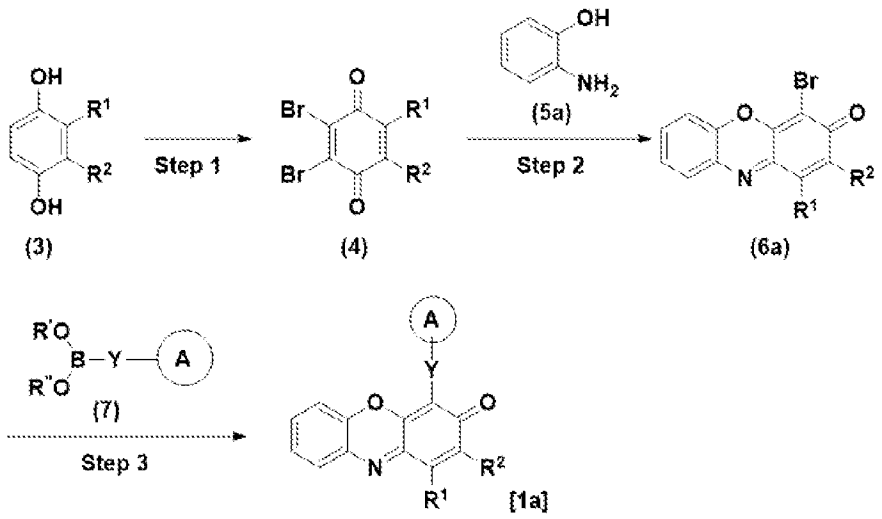
Production methods

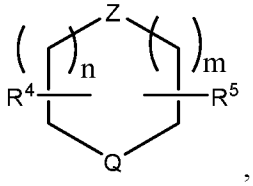
[00180] Compounds represented by Formula I or salts thereof are produced, in some embodiments, by methods described below.

Scheme 1A



Scheme 1B



[00181] It should be noted that R^{41} and R^{42} in compound (7) indicate a hydrogen atom, or an optionally substituted $C_{1\text{-}3}$ alkyl group, or R^{41} and R^{42} may be taken together to form a 5 to 7-membered carbocycle. In compounds (7), (1), and (1a),  indicates  , as defined above. Other symbols indicate the groups defined above.

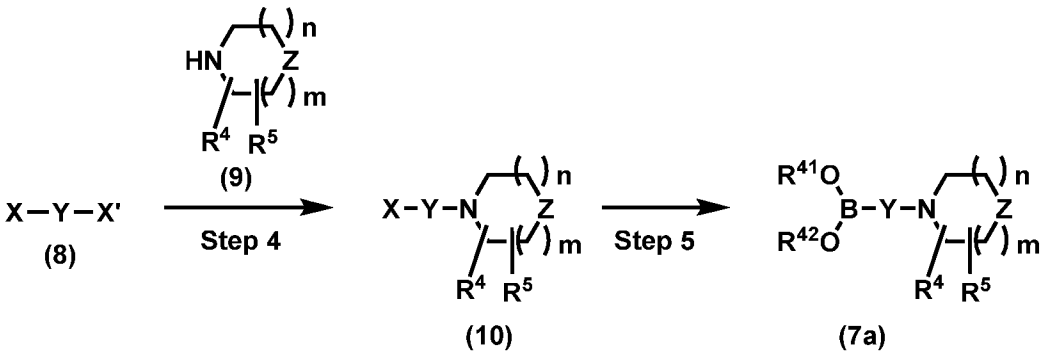
[00182] Step 1 is production step of Compound (4) by oxidation and bromination of commercially available compound (3). This step is performed according to a known procedure (For example, Bull. Chem. Soc. Jpn. 64, 336-338).

[00183] Step 2 is production step of Compound (6) or (6a) by reacting Compound (4) with commercially available Compound (5) or (5a), respectively. This step is performed by reacting Compound (4) with Compound (5) or (5a) in the presence of a base. The base is selected from bases and the like illustrated below, however, examples thereof preferably include potassium carbonate. A solvent used in the present step is selected from solvent and the like illustrated below, in some embodiments, acetonitrile. The present step is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours.

[00184] Step 3 is production step of Compound (1) or (1a) by reacting Compound (6) or (6a), respectively, with commercially available, or produced in Scheme 2 illustrated below Compound (7). This step is performed by reacting Compound (6) or (6a) with Compound (7) in the presence of a catalyst and a base. In some embodiments, the catalyst can include transition metals, such as palladium and the like, salts thereof, complexes thereof, those having them supported on a support, such as polymer and the like. The base is selected from bases and the like illustrated below; in some embodiments, it is selected from the group consisting of potassium carbonate, and cesium carbonate. A solvent used in the present step is selected from solvents and the like illustrated below, in some embodiments, a mixed solvent of 1,2-dimethoxyethane and water. The present step is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours.

[00185] Compound (7a) is produced, in some embodiments, by methods described below.

Scheme 2



[00186] It should be noted that X and X' in Compound (8) and Compound (10) indicate different halogen atoms, respectively. R^{41} and R^{42} in compound (7a) indicate a hydrogen

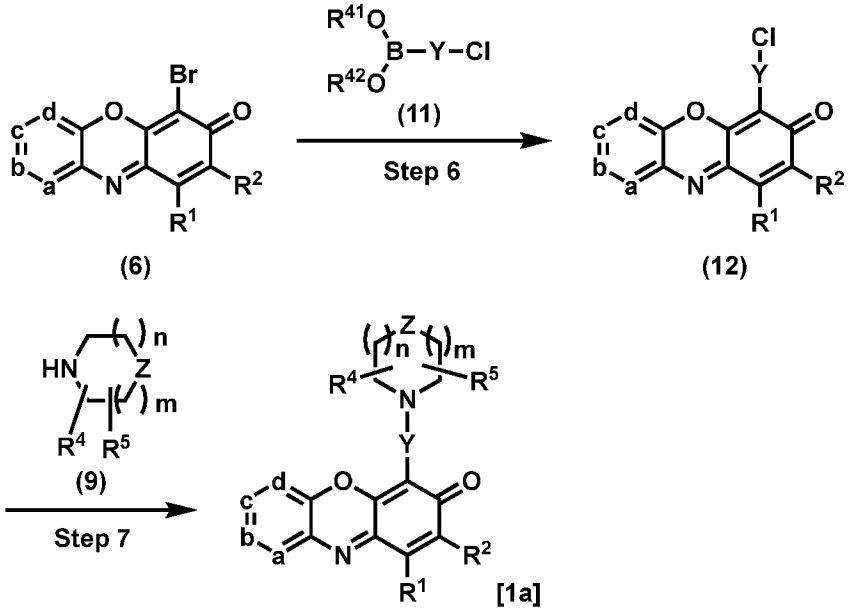
atom, or an optionally substituted C_{1-3} alkyl group, or R^{41} and R^{42} may be taken together to form a 5 to 7-membered carbocycle. Other symbols indicate the groups defined above.

[00187] Step 4 is production step of Compound (10) by reacting commercially available Compound (8) with commercially available Compound (9). This step is performed by reacting Compound (8) with Compound (9) in the presence of a catalyst, a base and an additive. In some embodiments, the catalyst can include transition metals, such as palladium and the like, salts thereof, complexes thereof, those having them supported on a support, such as polymer and the like. The additive is selected from bases and the like illustrated below, in some embodiments 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). The base is selected from bases and the like illustrated below; in some embodiments, the base is selected from the group consisting of sodium t-butoxide, and potassium t-butoxide. A solvent used in the present step is selected from solvents and the like illustrated below, in some embodiments toluene. The present step is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours.

[00188] Step 5 is production step of Compound (7a) by boronation reaction of Compound (10). This step is performed by reacting Compound (10) in the presence of a boronic acid, or a boronate source, a catalyst, an additive and a base. In some embodiments, boronic acid, or a boronate source is selected from examples, pinacol boran, 4,4,6-trimethyl-1,3,2-dioxaborinan, isopropoxyboronic acid pinacol ester, bis(pinacolato)diboran and bis(neopentylglycolato)diboran; in some embodiments bis(pinacolato)diboran. In some embodiments, the catalyst can include transition metals, such as palladium and the like, salts thereof, complexes thereof, those having them supported on a support, such as polymer and the like. The additive is selected from bases and the like illustrated below, in some embodiments XPhos. A base is selected from bases and the like illustrated below, in some embodiments potassium acetate. In some embodiments, solvent used in the present step is selected from solvents and the like illustrated below, and in some embodiments is 1,4-dioxane, or cyclopentylmethyl ether. The present step is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours.

[00189] In some embodiments, methods for preparing compounds represented by Formula (I) or salts thereof are described below.

Scheme 3



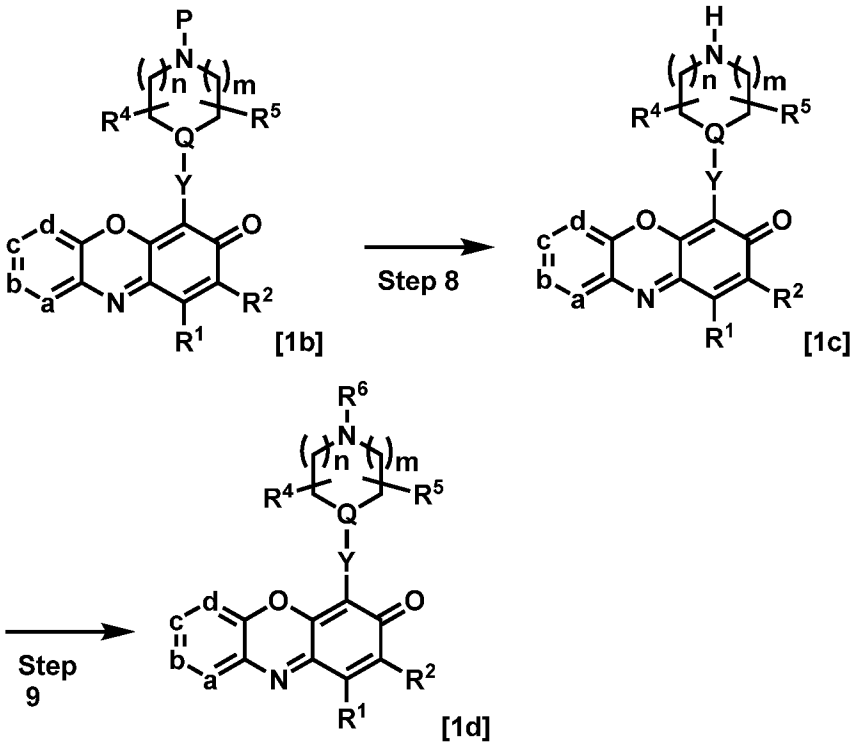
[00190] R^{41} and R^{42} in compound (7a) indicate a hydrogen atom, or an optionally substituted C_{1-3} alkyl group, or R^{41} and R^{42} may be taken together to form a 5 to 7-membered carbocycle. Other symbols indicate the groups defined above.

[00191] Step 6 is production step of Compound (12) by reacting Compound (6) and commercially available Compound (11). This step is performed according to the procedure described in Step 3.

[00192] Step 7 is production step of Compound (1a) by reacting Compound (12) and commercially available Compound (9). This step is performed according to the procedure described in Step 4.

[00193] In some embodiments, methods for preparing compounds represented by Formula (I) or salts thereof are described below.

Scheme 4



[00194] It should be noted that P in Compound (1b) indicates a protecting group. Other symbols indicate the groups defined above.

[00195] Step 8 is production step of Compound (1c) by deprotection reaction of the protecting group on amino group on Compound (1b). This step is performed according to a known procedure, for example, described in Greene's Protective Groups in Organic Synthesis, Forth Edition (T. W. Greene et al., Wiley, 2009).

[00196] Step 9 is production step of Compound (1d) by introduction of a substituent group to the amino group on Compound (1c). This step is performed by alkylation reaction, reductive amination reaction, acylation reaction and condensation reaction of Compound (1c). Alkylation reaction is performed by Compound (1c) with an appropriate alkylation agent and a base. In some embodiments, the base is selected from bases and the like illustrated below; in some embodiments, the base is selected from the group consisting of potassium carbonate, and cesium carbonate. In some embodiments, solvent used in the present step is selected from solvents and the like illustrated below, in some embodiments, acetonitrile. This reaction is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours. Reductive amination reaction is performed by Compound (1c) with an appropriate carbonyl compound and a base. In some embodiments, a base is selected from

examples, including sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride and pyridine-boran complex, and in some embodiments is sodium triacetoxybrohydride. In some embodiments, a solvent used in the present step is selected from solvents and the like illustrated below, in some embodiments, dichloromethane. Acetic acid can be added as necessary. This reaction is carried out at 0 to 150°C, in some embodiments, within a range of 0.5 to 24 hours. Acylation reaction is performed by Compound (1c) with an appropriate acylation agent and a base. In some embodiments, a base is selected from bases and the like illustrated below, and in some embodiments is diisopropylethylamine. In some embodiments a solvent used in the present step is selected from solvents and the like illustrated below, and in some embodiments istetrahydrofuran. This reaction is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours. Condensation reaction is performed by Compound (1c) with an appropriate carboxylic acid, a condensation agent and a base. In some embodiments, a condensation agent is selected from, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, dicyclohexylcarbodiimide, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 1-hydroxybenzotriazole. In some embodiments, a base is selected from bases and the like illustrated below, and in some embodiments is diisopropylethylamine. In some embodiments, a solvent used in the present step is selected from solvents and the like illustrated below, and in some embodiments is dichloromethane. This reaction is carried out at 0 to 150 °C, in some embodiments, within a range of 0.5 to 24 hours.

[00197] Bases used in the above schemes 1-4 should be appropriately selected depending on the types of reaction and raw material compound, and the like. Examples thereof include alkali bicarbonates such as sodium bicarbonate and potassium bicarbonate; alkali carbonates such as sodium carbonate and potassium carbonate; metal hydrides such as sodium hydride and potassium hydride; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; alkali metal alkoxides such as sodium methoxide and sodium t-butoxide; organic metal bases such as butyl lithium and lithium diisopropylamide; organic bases such as triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine (DMAP), and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU).

[00198] Solvents used in the above scheme 1-4 should be appropriately selected depending on the types of reaction and raw material compound, and the like. In some embodiments, the solvents are alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and

ethyl methyl ketone; halogenated hydrocarbons such as methylene chloride and chloroform; ethers such as tetrahydrofuran (THF), dioxane, 1,2-dimethoxyethane; aromatic hydrocarbons such as toluene and benzene; aliphatic hydrocarbons such as hexane and heptane; esters such as ethyl acetate and propyl acetate; amides such as N,N-dimethylformamide (DMF) and N-methyl-2-pyrrolidone; sulfoxides such as dimethyl sulfoxide (DMSO); nitriles such as acetonitrile. These solvents can be used alone or as a mixture of two or more thereof. In addition, according to the type of reaction, organic bases may be used as solvent.

[00199] An additive used in the above scheme 2 should be appropriately selected depending on the types of reaction and raw material compound, and the like. Some embodiments thereof include the phosphine ligands described in the literature, Aldrichimica Acta 39, 17-26, 2006.

[00200] The compound described herein represented by formula (I) or an intermediate thereof can be separated and purified by a known method to those skilled in the art. Some embodiments thereof include extraction, distribution, reprecipitation, column chromatography (e.g., silica gel column chromatography, ion exchange column chromatography, preparative liquid chromatography, and the like), recrystallization, and the like. The following can be used as recrystallization solvent: in some embodiments, alcohol-based solvent such as methanol, ethanol, 2-propanol, and the like; ether-based solvent such as diethyl ether and the like; ester-based solvent such as ethyl acetate and the like; aromatic-hydrocarbon-based solvent such as benzene, toluene, and the like; ketone-based solvent such as acetone and the like; halogen-based solvent such as dichloromethane, chloroform, and the like; hydrocarbon-based solvent such as hexane and the like; aprotic solvent such as dimethylformamide, acetonitrile, and the like; water; or mixed solvent of two or more selected from the above solvents. Other purification methods can be used, such as methods described in *Jikken Kagaku Koza* (The Chemical Society of Japan ed., Maruzen), vol. 1, or the like.

[00201] In the compounds described herein represented by formula (I) or pharmaceutically acceptable salts thereof, asymmetry may occur, or it may have a substituent having an asymmetric carbon. In such compounds, optical isomers are present. The compound described herein also encompasses mixtures of these respective isomers, and isolated isomers, and can be produced according to a general production method. Specific examples of the production method include a method using a raw material having an asymmetric point, a method in which asymmetry is introduced half way, a method of performing optical

resolution or the like in a suitable stage of a production step, and the like. Examples of optical resolution methods include a diastereomer method of forming a salt, when the compound represented by formula (I) or intermediates therefor have a basic functional group, in inactive solvent (alcohol-based solvent such as methanol, ethanol, 2-propanol, and the like; ether-based solvent such as diethyl ether and the like; ester-based solvent such as ethyl acetate and the like; hydrocarbon-based solvent such as toluene and the like; aprotic solvent such as acetonitrile and the like; or mixed solvent of two or more selected from the above solvents) using an optically active acid (e.g., monocarboxylic acid such as mandelic acid, N-benzyloxy-alanine, lactic acid, and the like, dicarboxylic acid such as tartaric acid, o-di-isopropylidene tartaric acid, malic acid, and the like, sulfonic acid such as camphor sulfonic acid, bromocamphorsulfonic acid, and the like). When an intermediate for the compound described herein represented by formula (I) has an acidic functional group such as a carboxyl group and the like, optical resolution also can be performed by a diastereomer method of forming a salt using an optically active amine (e.g., organic amines such as 1-phenylethylamine, quinine, quinidine, cinchonidine, cinchonine, strychnine, and the like).

[00202] A temperature to form a salt in the diastereomer methods is selected from the range from -50°C to the boiling point of solvent, preferably the range from 0°C to the boiling point, and more preferably the range from room temperature to the boiling point of solvent. To improve the optical purity, it is desirable to increase a temperature to the vicinity of the boiling point of a solvent once. When a precipitated salt is collected by filtration, as necessary, it can be cooled to improve the yield. Regarding the amount of an optically active acid or amine used, the range from about 0.5 to about 2.0 equivalents, preferably the range of approximately 1 equivalent, relative to a substrate is suitable. As necessary, crystal can be recrystallized in inactive solvent (e.g., alcohol-based solvent such as methanol, ethanol, 2-propanol, and the like; ether-based solvent such as diethyl ether and the like; ester-based solvent such as ethyl acetate and the like; hydrocarbon-based solvent such as toluene and the like; aprotic solvent such as acetonitrile and the like; or mixed solvent of two or more selected from the above solvents) to obtain an optically active salt in high purity. In addition, a salt that is optically resolved as necessary can be treated with an acid or a base by a general method to obtain its free form.

[00203] Among starting materials and intermediates in respective production methods described above, those of which production methods are not particularly and repeatedly

described are commercially available compounds or can be synthesized from a commercially available compound by a known method to those skilled in the art or a method in accordance therewith.

[00204] Hereinafter, the present disclosure is more specifically described with reference examples, Examples, and test examples. However, the scope of the present invention is certainly not limited to these examples. It should further be noted that compound names shown in the following reference examples and Examples do not always follow the IUPAC nomenclature.

EXAMPLES

[00205] The disclosure is further described by the following non-limiting examples and embodiments. The following examples are given for the purpose of illustrating various embodiments of the present disclosure and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods described herein, are presently representative of preferred cases, are exemplary, and are not intended as limitations on the scope of the present disclosure. Changes therein and other uses which are encompassed within the spirit of the present disclosure as defined by the scope of the claims will occur to those skilled in the art.

Synthesis of Compounds

[00206] The following abbreviations are sometimes used throughout the present specification: Me: methyl, tert: tertiary, Boc: tert-butoxycarbonyl, s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quartet, dd: doubled doublet, m: multiplet, J: coupling constant, Hz: Hertz, $CDCl_3$: deuterated chloroform.

[00207] For silica gel column chromatography and amino silica gel column chromatography used in Reference Examples and Examples, a silica gel column and an amino silica gel column produced by Yamazen Corporation were used. Measurement by LC-MS was carried out using various conditions shown below in Table 1. Retention time (R.T.) represents the time when a mass spectrum peak appeared in LC-MS measurements.

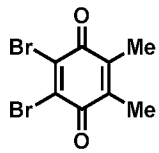
Table 1. LC-MS conditions.

	Analysis condition
Analyzer	WATERS ACQUITY UPLC (Registered trademark) equipment

	Analysis condition
Column	ACQUITY UPLC BEH C18 Column, 130Å, 1.7 μm, 2.1 mm X 150 mm
Solvent	Solution A: 0.05% formic acid in H_2O Solution B: acetonitrile
Gradient condition	0.0 min to 1.3 min; A/B 90:10~1:99 1.3 min to 1.5 min; A/B 1:99 1.5 min to 2.0 min; A/B 90:10
Flow rate	0.75 mL/min
Wavelength (UV)	220 nm, 254 nm
Column temperature	40°C

[00208] Unless otherwise specified, for raw material compounds, reaction reagents, and solvents, those commercially available were used.

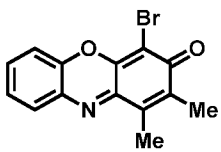
Reference Example 1. 2,3-dibromo-5,6-dimethylcyclohexa-2,5-diene-1,4-dione



[00209] 2,3-dimethylbenzene-1,4-diol (2.0 g, 1.45 mmol) was dissolved in acetic acid (36 mL) and H_2O (72 mL). To this solution, benzyltrimethylammonium tribromide (25.4 g, 65.1 mmol) was added and stirred for 5 h at 60°C. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was used in the next reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 2.11 (6H, s).

Reference Example 2. 4-bromo-1,2-dimethyl-3*H*-phenoxazin-3-one



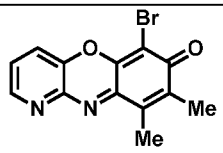
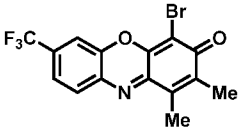
[00210] Reference Example 1, potassium carbonate (6.0 g, 43.5 mmol), and 2-aminophenol (4.74 g 43.4 mmol) were dissolved in acetonitrile (140 mL) and the reaction mixture was

stirred for 3h at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the compound of Reference Example 2 (3.0 g, 2 steps, 69%). ^{1}H-NMR ($CDCl_3$) δ: 7.83 (1H, dd, J = 8.0, 1.6 Hz), 7.56-7.53 (1H, m), 7.45 (1H, dd, J = 8.3, 0.9 Hz), 7.40-7.36 (1H, m), 2.45 (3H, s), 2.24 (2H, s).
LC-MS: R.T. 1.29, m/z 305 (M+1).

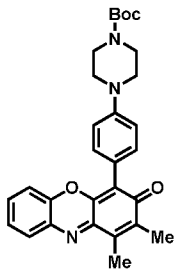
Reference Examples 3 and 4

[00211] In accordance with the method described in Reference Example 2, Reference Examples 3 and 4 shown in the following table were obtained using corresponding raw materials.

Table 2.

Reference Example	**Structure**	**NMR, LCMS**
3		LC-MS R.T. 0.95 min, m/z 305 (M+1).
4		^{1}H-NMR ($CDCl_3$) δ: 7.94 (1H, d, J = 8.3 Hz), 7.71 (1H, s), 7.61 (1H, d, J = 8.3 Hz), 2.44 (3H, s), 2.25 (3H, s). LC-MS R.T. 1.40 min, m/z 373 (M+1).

Example 1. Tert-butyl 4-[4-(1,2-dimethyl-3-oxo-3*H*-phenoxazin-4-yl)phenyl]piperazine-1-carboxylate

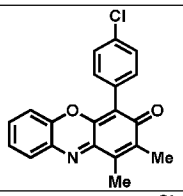
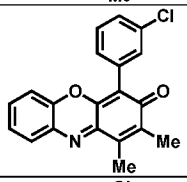
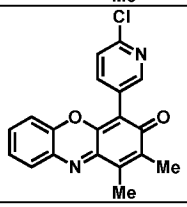


[00212] Reference Example 2 (1.19 g, 3.93 mmol), 4-[4-(tert-butoxycarbonyl)piperazin-1-yl]phenylboronic acid pinacol ester (1.83 g, 4.71 mmol), 1,1'-

bis(diphenylphosphino)ferrocene palladium(II) dichloride dichoromethane adduct (481 mg, 0.48 mmol) and cesium carbonate (2.56 g, 7.86 mmol) were dissolved in a mixed solution of 1,2-dimethoxyethane (35 mL) and H_2O (7 mL), and the reaction mixture was stirred for 3 h at 90°C. The reaction mixture was filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the compound of Example 1 (1.22 g, 64%). ^{1}H-NMR ($CDCl_3$) δ: 7.84-7.71 (1H, m), 7.52-7.10 (5H, m), 7.03-6.91 (2H, m), 3.58 (4H, s), 3.20 (4H, s), 2.47 (3H, s), 2.21 (3H, s), 1.53 (9H, s).
LC-MS: R.T. 1.52 min, m/z 486 (M+1).

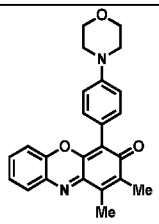
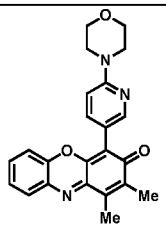
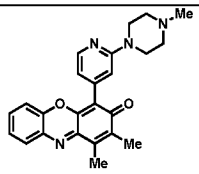
[00213] In accordance with the method described in Example 1, Reference Examples 5 to 7 shown in the following table were obtained using the compound of Reference Example 2 and corresponding raw materials.

Table 3.

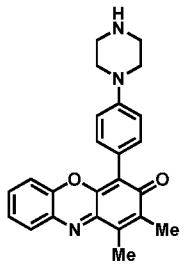
Reference Example	Structure	NMR, LCMS
5		LC-MS R.T. 1.21min, m/z 337 (M+1).
6		^{1}H-NMR ($CDCl_3$) δ: 7.80 (1H, dd, J = 8.0, 1.7 Hz), 7.46-7.42 (1H, m), 7.39-7.30 (4H, m), 7.18 (1H, dd, J = 8.3, 1.5 Hz), 6.97-6.93 (2H, m), 2.49 (3H, d, J = 1.0 Hz), 2.22 (3H, d, J = 1.0 Hz).
7		LC-MS R.T. 1.34min, m/z 338 (M+1).

[00214] In accordance with the method described in Example 1, Examples 2-4 shown in the following table were obtained using the compound of Reference Example 2 and corresponding raw materials.

Table 4.

Example	Structure	NMR, LCMS
2		^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 7.8, 1.4 Hz), 7.43-7.37 (3H, m), 7.30-7.26 (1H, m), 7.15 (1H, dd, J = 8.3, 0.9 Hz), 6.99-6.96 (2H, m), 3.88-3.86 (4H, m), 3.24-3.22 (4H, m), 2.47 (3H, d, J = 0.9 Hz), 2.21 (3H, d, J = 0.9 Hz). LC-MS R.T. 1.31 min, m/z 387 (M+1).
3		^{1}H-NMR ($CDCl_3$) δ: 8.38 (1H, d, J = 2.4 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.66 (1H, dd, J = 8.8, 2.4 Hz), 7.42 (1H, t J = 7.8 Hz), 7.32-7.19 (2H, m), 6.72 (1H, d, J = 8.8 Hz), 3.87-3.82 (4H, m), 3.59-3.55 (4H, m), 2.48 (3H, s), 2.21 (3H, s). LC-MS R.T. 1.05 min, m/z 338 (M+1).
4		^{1}H-NMR ($CDCl_3$) δ: 8.26 (1H, d, J = 5.0 Hz), 7.82-7.79 (1H, m), 7.47-7.42 (1H, m), 7.33 (1H, t, J = 7.6 Hz), 7.17 (1H, d, J = 8.3 Hz), 6.73 (2H, s), 6.69 (2H, d, J = 5.0 Hz), 3.60 (4H, s), 2.54 (4H, s), 2.49 (3H, s), 2.21 (3H, s).

Example 5. 1,2-dimethyl-4-[4-(piperazin-1-yl)phenyl]-3*H*-phenoxazin-3-one

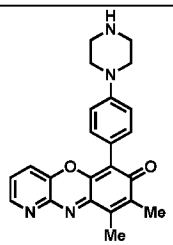
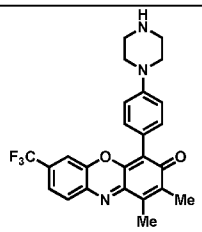
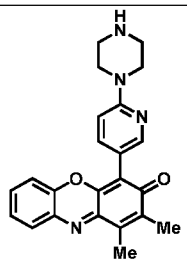
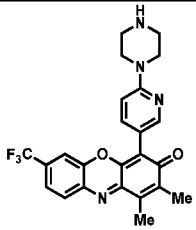


[00215] Example 1 (788 mg, 1.62 mmol) was dissolved in chloroform (15 mL). To this solution, trifluoroacetic acid (3 mL) was added and stirred for 4 h at room temperature. The reaction mixture was evaporated and purified by amino silica gel column chromatography to afford the compound of Example 5 (460 mg, 74%).

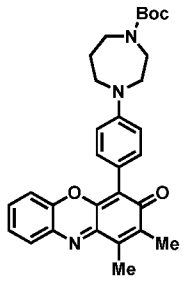
^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, d, J = 7.8 Hz), 7.39 (3H, d, J = 8.3 Hz), 7.30-7.25 (1H, m), 7.16 (1H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 3.25-3.21 (4H, m), 3.07-3.03 (4H, m), 2.47 (3H, s), 2.21 (3H, s). LC-MS: R.T. 0.87 min, m/z 386 (M+1).

[00216] In accordance with the method described in Example 5, Examples 6 to 9 shown in the following table were obtained using the compounds of Reference Examples 2 to 4 and corresponding raw materials.

Table 5.

Example	Structure	NMR, LCMS
6		^{1}H-NMR ($CDCl_3$) δ: 8.54 (1H, dd, J = 4.5, 1.6 Hz), 7.50 (1H, dd, J = 8.2, 1.6 Hz), 7.39-7.32 (3H, m), 6.08 (2H, d, J = 9.0 Hz), 3.34-3.30 (4H, m), 2.65-2.59 (4H, m), 2.53 (3H, s), 2.22 (3H, s). LC-MS R.T. 0.65 min, m/z 387 (M+1).
7		^{1}H-NMR ($CDCl_3$) δ: 7.84 (1H, d, J = 8.3 Hz), 7.49 (1H, d, J = 8.3 Hz), 7.40-7.35 (3H, m), 6.98 (2H, d, J = 8.8 Hz), 3.25-3.21 (4H, m), 3.05-3.02 (4H, m), 2.45 (3H, s), 2.21 (3H, s). LC-MS R.T. 0.91 min, m/z 454 (M+1).
8		^{1}H-NMR ($CDCl_3$) δ: 8.39-8.36 (1H, m), 7.77 (1H, dd, J = 8.0, 1.6 Hz), 7.64 (1H, dd, J = 8.9, 2.5 Hz), 7.44-7.38 (1H, m), 7.32-7.19 (2H), 6.73 (1H, d, J = 9.2 Hz), 3.62-3.59 (4H, m), 3.04-3.01 (4H, m), 2.47 (3H, s), 2.21 (3H, s). LC-MS R.T. 0.75 min, m/z 386 (M+1).
9		^{1}H-NMR ($CDCl_3$) δ: 8.35 (1H, d, J = 2.3 Hz), 7.85 (1H, d, J = 7.8 Hz), 7.61 (1H, dd, J = 9.0, 2.3 Hz), 7.51 (1H, d, J = 78 Hz), 7.46 (1H, s), 6.73 (1H, d, J = 8.8 Hz) LC-MS R.T. 0.87 min, m/z 455 (M+1).

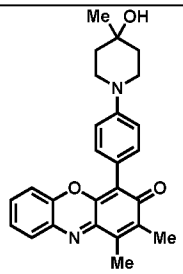
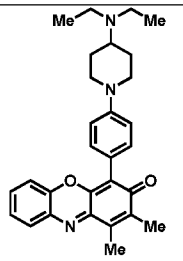
Reference Example 8. tert-butyl 4-[4-(1,2-dimethyl-3-oxo-3*H*-phenoxazin-4-yl)phenyl]-1,4-diazepane-1-carboxylate



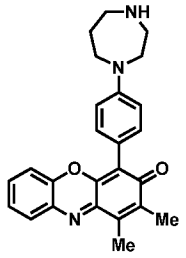
[00217] Reference Example 5 (150 mg, 0.45 mmol), 1-Boc-hexahydro-1,4-diazepine (134 mg, 0.67 mmol), Tris(dibenzylideneacetone)dipalladium(0) (41 mg, 0.05 mmol), XPhos (43 mg, 0.09 mmol) and sodium tert-butoxide (129 mg, 1.34 mmol) were dissolved in toluene (3 mL), and the reaction mixture was stirred for 1.5 h at 90°C. The reaction mixture was diluted with water and extracted with EtAOc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by silica gel column chromatography to afford the compound of Reference Example 8 (52 mg, 23%). ^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, dd, J = 8.3, 1.4 Hz), 7.41-7.37 (3H, m), 7.28-7.24 (1H, m), 7.18-7.16 (1H, m), 6.77-6.74 (2H, m), 3.60-3.57 (8H, m), 2.46 (3H, s), 2.21 (3H, s), 2.01-1.98 (2H, m), 1.56 (9H, s).

[00218] In accordance with the method described in Reference Example 8, Examples 10 and 11 shown in the following table were obtained using the compound of Reference Example 5 and corresponding raw materials.

Table 6.

Example	Structure	NMR, LCMS
10		LC-MS R.T. 1.03 min, m/z 416 (M+1).
11		^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, dd, J = 8.3, 2.0 Hz), 7.41-7.35 (3H, m), 7.29-7.24 (1H, m), 7.15 (1H, dd, J = 8.0, 1.2 Hz), 6.99-6.96 (2H, m), 3.85-3.82 (2H, m), 2.79-2.56 (7H, m), 2.46 (3H, d, J = 0.7 Hz), 2.20 (3H, d, J = 0.7 Hz), 1.88-1.84 (2H, m), 1.72-1.62 (2H, m), 1.65 (6H, t, J = 7.1 Hz). LC-MS R.T. 0.84 min, m/z 457 (M+1).

Example 12. 4-[4-(1,4-diazepan-1-yl)phenyl]-1,2-dimethyl-3*H*-phenoxazin-3-one

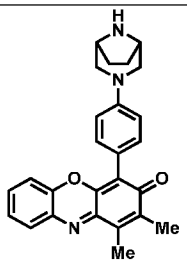
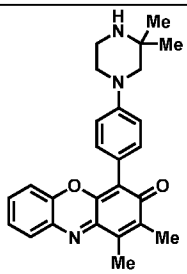


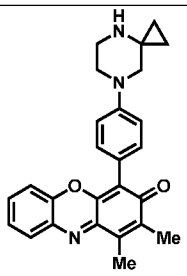
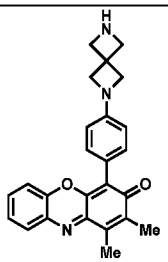
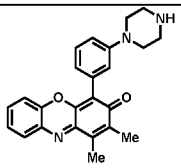
[00219] In accordance with the method described in Example 5, Example 12 was obtained using the compound of Reference Example 8. ^{1}H-NMR ($CDCl_3$) δ: 7.74 (1H, dd, J = 7.8, 1.8 Hz), 7.40-7.36 (3H, m), 7.28-7.24 (1H, m), 7.17 (1H, dd, J = 8.3, 1.4 Hz), 6.77-6.75 (2H, m), 3.63-3.58 (4H, m), 3.06-3.04 (2H, m), 2.87-2.84 (2H, m), 2.46 (3H, d, J = 0.9 Hz), 2.20 (3H, d, J = 0.9 Hz), 1.94-1.88 (2H, m).

LC-MS: R.T. 0.82 min, m/z 400 (M+1).

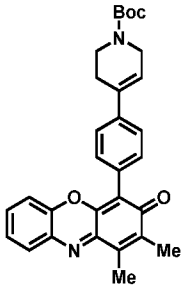
[00220] In accordance with the method described inEexample 12, Examples 13 to 17 shown in the following table were obtained using the compounds of Reference Examples 5 and 6 and corresponding raw materials.

Table 7.

Example	Structure	NMR, LCMS
13		1H-NMR (CDCl3) δ: 7.75 (1H, dd, J = 7.8, 1.4 Hz), 7.41-7.36 (3H, m), 7.28-7.24 (1H, m), 7.17 (1H, dd, J = 8.3, 1.4 Hz), 6.87-6.85 (2H, m), 3.65-3.64 (2H, m), 3.53-3.50 (2H, m), 2.97-2.93 (2H, m), 2.46 (3H, d, J = 0.9 Hz), 2.20 (3H, d, J = 0.9 Hz), 1.88-1.80 (4H, m). LC-MS R.T. 0.83 min, m/z 413 (M+1).
14		^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 7.8, 1.4 Hz), 7.41-7.36 (3H, m), 7.29-7.25 (1H, m), 7.16 (1H, dd, J = 8.3, 1.4 Hz), 6.97-6.93 (2H, m), 3.17-3.13 (2H, m), 3.09-3.05 (2H, m), 2.97 (2H, s), 2.46 (3H, d, J = 0.9 Hz), 2.21 (3H, d, J = 0.9 Hz), 1.23 (6H, s). LC-MS R.T. 0.82 min, m/z 415 (M+1).

Example	Structure	NMR, LCMS
15		^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, dd, J = 7.8, 1.4 Hz), 7.43-7.37 (3H, m), 7.29-7.25 (1H, m), 7.14 (1H, dd, J = 8.3, 0.9 Hz), 6.95-6.93 (2H, m), 3.23-3.20 (2H, m), 3.14-3.11 (2H, m), 3.04 (2H, s), 2.46 (3H, d, J = 0.9 Hz), 2.21 (3H, d, J = 0.9 Hz), 0.71-0.60 (4H, m). LC-MS R.T. 0.81 min, m/z 413 (M+1).
16		^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, dd, J = 7.8, 1.4 Hz), 7.40-7.32 (3H, m), 7.30-7.24 (1H, m), 7.14 (1H, dd, J = 8.3, 0.9 Hz), 6.53-6.50 (2H, m), 4.02 (4H, s), 3.80 (4H, s), 2.46 (3H, d, J = 0.9 Hz), 2.20 (3H, d, J = 0.9 Hz). LC-MS R.T. 0.80 min, m/z 398 (M+1).
17		^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, dd, J = 8.0, 1.7 Hz), 7.42-7.27 (3H, m), 7.14 (1H, dd, J = 8.0, 1.2 Hz), 6.99-6.91 (3H, m), 3.18-3.16 (4H, m), 3.03-3.01 (4H, m), 2.48 (3H, d, J = 1.0 Hz), 2.22 (3H, d, J = 1.0 Hz). LC-MS R.T. 0.77 min, m/z 386 (M+1).

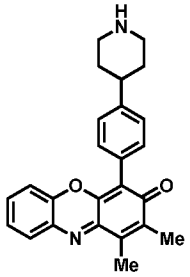
Reference Example 9. tert-butyl 4-[4-(1,2-dimethyl-3-oxo-3*H*-phenoxazin-4-yl)phenyl]-3,6-dihydropyridine-1(2*H*)-carboxylate



[00221] Reference Example 5 (120 mg, 0.36 mmol), 1-boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (133 mg, 0.43 mmol), Tris(dibenzylideneacetone)dipalladium(0) (16 mg, 0.02 mmol), XPhos (17 mg, 0.04 mmol) and tripotassium phosphate (115 mg, 0.54 mmol) were dissolved in toluene (2 mL), and the reaction mixture was stirred for 4 h at 90°C. The reaction mixture was purified by silica gel column chromatography to afford the compound of Reference Example 9 (89 mg, 52%).

LC-MS: R.T. 1.60 min, m/z 483 (M+1).

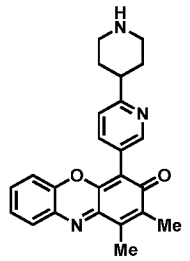
Example 18. 1,2-dimethyl-4-[4-(piperidin-4-yl)phenyl]-3*H*-phenoxazin-3-one



[00222] Reference Example 9 (89 mg, 0.18 mmol) and 10% Pd/C (40 mg) were dissolved in EtOH (2 mL), and the reaction mixture was stirred for overnight at room temperature under H_2 atmosphere. The reaction mixture was filtrated and evaporated. To this residue, chloroform (2 mL) and trifluoroacetic acid (1 mL) were added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated and purified by amino silica gel column chromatography to afford the compound of Example 18 (32 mg, 45%). ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, d, J = 6.3 Hz), 7.40 (3H, d, J = 8.0 Hz), 7.33-7.26 (3H, m), 7.18 (1H, d, J = 8.3 Hz), 3.20 (2H, d, J = 12.4 Hz), 2.80-2.62 (3H, m), 2.48 (3H, s), 2.21 (3H, s), 1.93-1.85 (2H, m), 1.73-1.63 (2H m).

LC-MS: R.T. 0.89 min, m/z 385 (M+1).

Example 19. 1,2-dimethyl-4-[6-(piperidin-4-yl)pyridin-3-yl]-3*H*-phenoxazin-3-one

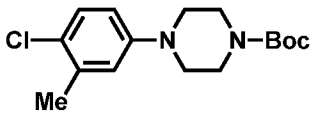


[00223] In accordance with the method described in Example 18, Example 19 was obtained using the compound of Reference Example 7 and corresponding raw materials.

^{1}H-NMR ($CDCl_3$) δ: 8.66 (1H, d, J = 2.2 Hz), 7.80 (1H, dd, J = 7.9, 1.6 Hz), 7.75 (1H, dd, J = 8.0, 2.2 Hz), 7.46-7.41 (1H, m), 7.34-7.30 (1H, m), 7.27 (1H, d, J = 8.3 Hz), 7.20 (1H, dd, J = 8.2, 1.3 Hz), 3.23 (2H, d, J = 12.0 Hz), 2.93-2.85 (1H m), 2.82-2.74 (2H, m), 2.49 (3H, s), 2.22 (3H, s), 2.00 (2H, d, J = 16.3 Hz), 1.80-1.74 (2H).

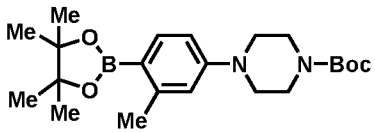
LC-MS: R.T. 0.81 min, m/z 386 (M+1).

Reference Example 10. tert-butyl 4-(4-chloro-3-methylphenyl)piperazine-1-carboxylate



[00224] 4-bromo-1-chloro-2-methylbenzene (1.5 g, 7.30 mmol), tert-butyl piperazine-1-carboxylate (1.36 g, 7.30 mmol), Tris(dibenzylideneacetone)dipalladium(0) (69 mg, 0.07 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (91 mg, 0.15 mmol) and sodium tert-butoxide (982 mg, 10.22 mmol) were dissolved in toluene (15 mL), and the reaction mixture was stirred overnight at 60°C. The reaction mixture was filtrated, diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the compound of Reference Example 10 (1.91 g, 84%). ^{1}H-NMR ($CDCl_3$) δ: 7.18 (1H, d, J = 8.5 Hz), 6.76 (1H, s), 6.67 (1H, d, J = 8.5 Hz), 3.57-3.53 (4H, m), 3.08-3.04 (4H, m), 2.31 (3H, s), 1.46 (9H, s).

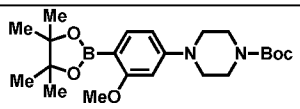
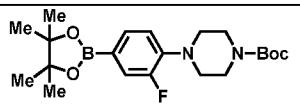
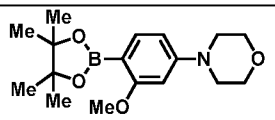
Reference Example 11. tert-butyl 4-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate



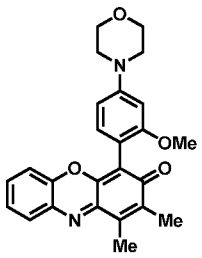
[00225] Reference Example 10 (1.91 g, 6.15 mmol), bis(pinacolato)diboran (2.34 g, 9.22 mmol), Tris(dibenzylideneacetone)dipalladium(0) (169 mg, 0.18 mmol), Xphos (176 mg, 0.37 mmol) and potassium acetate (1.81 g, 18.45 mmol) were dissolved in cyclopentylmethyl ether (20 mL), and the reaction mixture was stirred for 8 h at 110°C. The reaction mixture was filtrated and evaporated. The residue was purified by silica gel column chromatography to afford the compound of reference example 11 (2.33 g, 94%). ^{1}H-NMR ($CDCl_3$) δ: 7.67-7.62 (1H, m), 6.69 (2H, dd, J = 8.7, 6.2 Hz), 3.57-3.49 (4H, m), 3.22-3.14 (4H, m) 2.48 (3H, s), 1.46 (9H, s), 1.29 (12H, s).

[00226] In accordance with the method described in Reference Example 11, Reference Examples 12 to 14 shown in the following table were obtained using the corresponding raw materials.

Table 8.

Reference Example	Structure	NMR
12		^{1}H-NMR ($CDCl_3$) δ: 7.62-7.54 (1H, m), 6.50-6.29 (2H, m), 3.80 (3H, s), 3.66-3.48 (4H, m), 3.26-3.13 (4H, m), 1.46 (9H, s), 1.30 (12H, s).
13		^{1}H-NMR ($CDCl_3$) δ: 7.50-7.40 (2H, m), 6.88 (1H, t, J = 8.0 Hz), 3.59-3.55 (4H, m), 3.07-304 (4H, m), 1.46 (9H, s), 1.30 (12H, s).
14		^{1}H-NMR ($CDCl_3$) δ: 7.59 (1H, d, J = 8.3 Hz), 6.45 (1H, dd, J = 8.3, 2.3 Hz), 6.34 (1H, d, J = 2.3 Hz), 3.84-3.82 (4H, m), 3.80 (3H, s), 3.21-3.19 (4H, m), 1.31 (12H, s).

Example 20. 4-[2-methoxy-4-(piperazin-1-yl)phenyl]-1,2-dimethyl-3*H* -phenoxazin-3-one

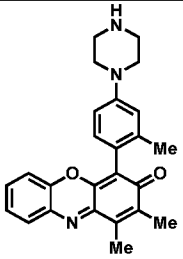
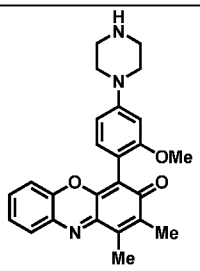
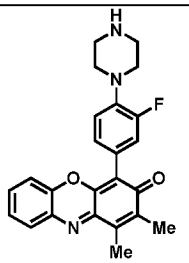


[00227] In accordance with the method described in Example 1, Example 20 was obtained using the compounds of Reference Examples 2 and 14. ^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 7.8, 1.4 Hz), 7.39-7.35 (1H, m), 7.27 (1H, dd, J = 7.8, 0.9 Hz), 7.13-7.09 (2H, m), 6.60-6.55 (2H, m), 3.89-3.84 (4H, m), 3.73 (3H, s), 3.25-3.22 (4H, m), 2.46 (3H, d, J = 0.9 Hz), 2.20 (3H, d, J = 0.9 Hz).

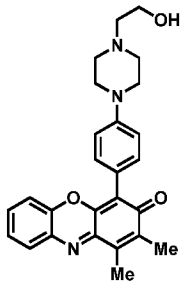
LC-MS: R.T. 1.25 min, m/z 417 (M+1).

[00228] In accordance with the method described in Example 5, Examples 21 to 23 shown in the following table were obtained using the compounds of Reference Examples 2, 11 to 13 and corresponding raw materials.

Table 9.

Example	Structure	NMR, LCMS
21		^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, m), 7.40-7.35 (1H, m), 7.31-7.26 (1H, m), 7.12 (1H, d, J = 8.3 Hz), 7.04 (1H, d, J = 8.3 Hz), 6.87-6.85 (1H, m), 6.84-6.80 (1H, m), 3.25-3.22 (4H, m), 3.08-3.05 (4H, m), 2.48 (3H, s), 2.21 (3H, s), 2.09 (3H, s). LC-MS R.T. 0.85 min, m/z 400 (M+1)..
22		^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 7.9, 1.5 Hz), 7.40-7.34 (1H, m), 7.29-7.25 (1H, m), 7.10 (2H, dd, J = 8.2, 1.9 Hz), 6.62-6.60 (1H, m), 6.58-6.55 (1H, m), 3.72 (3H, s), 3.25-3.21 (4H, m), 3.07-3.03 (4H, m), 2.46 (3H, s), 2.20 (3H, s). LC-MS R.T. 0.79 min, m/z 416 (M+1).
23		^{1}H-NMR ($CDCl_3$) δ: 7.80-7.77 (1H, m), 7.44-7.40 (1H, m), 7.33-7.28 (1H, m), 7.21-7.16 (3H, m), 7.00 (1H, t, J = 8.5 Hz), 3.15-3.11 (4H, m), 3.09-3.05 (4H, m), 2.47 (3H, s), 2.21 (3H, s). LC-MS R.T. 0.91 min, m/z 404 (M+1).

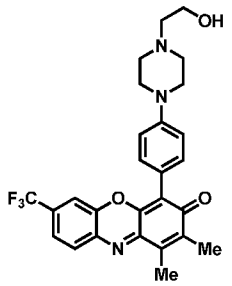
Example 24. 4-{4-[4-(2-hydroxyethyl)piperazin-1-yl]phenyl}-1,2-dimethyl-3*H*-phenoxazin-3-one



[00229] Example 5 (460 mg, 1.19 mmol), 2-bromoethanol (164 mg, 1.31 mmol) and potassium carbonate (197 mg, 1.43 mmol) were dissolved in acetonitrile (12 mL), and the reaction mixture was stirred overnight at 80°C. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the compound of Example 20 (312 mg, 61%). ^{1}H-NMR

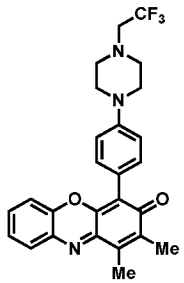
($CDCl_3$) δ: 7.76 (1H, dd, J = 7.9, 1.6 Hz), 7.42-7.37 (3H, m), 7.29-7.25 (1H, m), 7.17-7.14 (1H, m), 6.99-6.97 (2H, m), 3.66 (2H t, J = 5.4 Hz), 3.30-3.27 (4H, m), 2.71-2.67 (4H, m) 2.61 (2H, t, J = 5.4 Hz), 2.47 (3H, s), 2.21 (3H, s).
LC-MS: R.T. 0.90 min, m/z 431 (M+1).

Example 25. 4-{4-[4-(2-hydroxyethyl)piperazin-1-yl]phenyl}-1,2-dimethyl-7-(trifluoromethyl)-3*H*-phenoxazin-3-one



[00230] In accordance with the method described in Example 24, Example 25 was obtained using the compound of Example 7. ^{1}H-NMR ($CDCl_3$) δ: 7.84 (1H, d, J = 8.5 Hz), 7.51-7.48 (1H, m), 7.40-7.35 (3H, m), 6.99 (2H, d, J = 9.0 Hz), 3.68 (2H, t, J = 5.4 Hz), 3.34-3.31 (4H, m), 2.74-2.71 (4H, m), 2.65 (2H, t, J = 5.4 Hz), 2.46 (3H, s), 2.22 (3H, s).
LC-MS: R.T. 0.90 min, m/z 499 (M+1).

Example 26. 1,2-dimethyl-4-{4-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]phenyl}-3*H*-phenoxazin-3-one

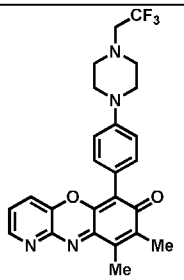
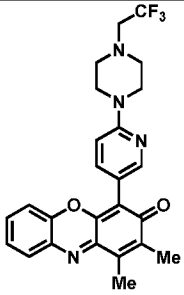
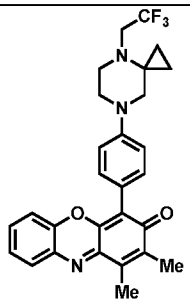
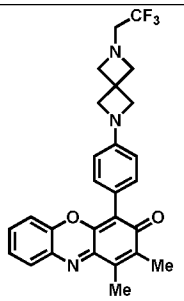


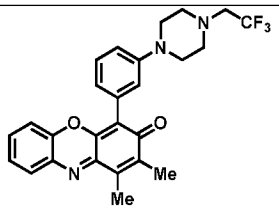
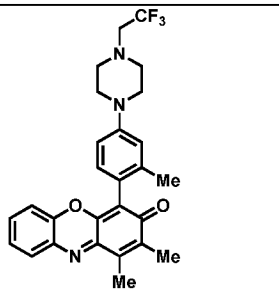
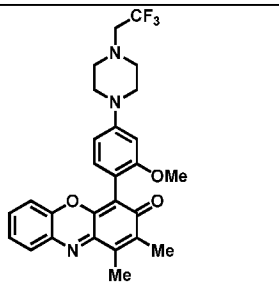
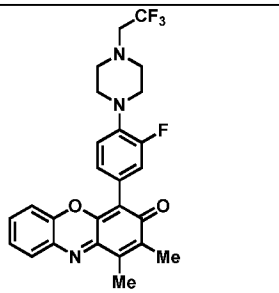
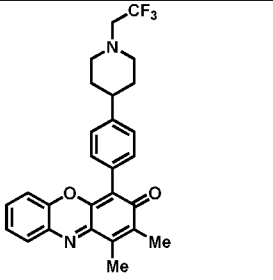
[00231] Example 5 (241 mg, 0.63 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (145 mg, 0.63 mmol) and potassium carbonate (174 mg, 1.26 mmol) were dissolved in acetonitrile (3 mL), and the reaction mixture was stirred for 3.5 h at 60°C. The reaction mixture was filtrated, evaporated and purified by silica gel column chromatography to afford the compound of Example 26 (107 mg, 37%) ^{1}H-NMR ($CDCl_3$) δ: 7.71 (1H, dd, J = 7.8, 1.4 Hz), 7.37-7.32 (3H, m), 7.25-7.21 (1H, m), 7.11 (1H, dd, J = 8.0, 1.1 Hz), 6.93 (2H d, J = 9.2

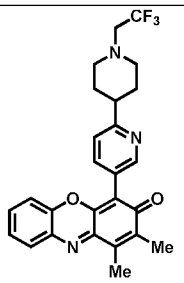
Hz), 3.25-3.22 (4H, m), 2.98 (2H, q, 9.5 Hz), 2.80-2.78 (4H, m), 2.42 (3H, s), 2.16 (3H, s). LC-MS: R.T. 1.49 min, m/z 468 (M+1).

[00232] In accordance with the method described in Example 26, Examples 27 to 36 shown in the following table were obtained using the compound of corresponding examples.

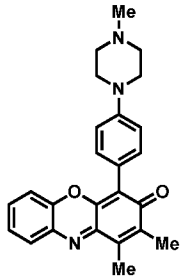
Table 10.

Ex	Structure	NMR, LCMS
27		^{1}H-NMR ($CDCl_3$) δ: 8.57-8.52 (1H, m), 7.55-7.46 (1H, m), 7.40-7.32 (3H, m), 7.05-6.95 (2H, m), 3.33-3.25 (4H, m), 3.08-2.99 (2H, m), 2.89-2.80 (4H, m), 2.53 (3H, s), 2.22 (3H, s). LC-MS R.T. 1.22 min, m/z 469 (M+1).
28		^{1}H-NMR ($CDCl_3$) δ: 8.37 (1H, d, J = 2.2 Hz), 7.77 (1H, dd, J = 7.9, 1.6 Hz), 7.65 (1H, dd, J = 8.9, 2.3 Hz), 7.44-7.39 (1H, m), 7.31-7.27 (1H, m), 7.22-7.19 (1H, m), 6.72 (1H, d, J = 8.8 Hz), 3.66-3.63 (4H, m), 3.03 (2H, q, J = 9.6 Hz), 2.81-2.78 (4H, m), 2.47 (3H, s), 2.21 (3H, s). LC-MS R.T. 1.28 min, m/z 469 (M+1).
29		^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 7.8, 1.4 Hz), 7.42-7.37 (3H, m), 7.30-7.26 (1H, m), 7.14 (1H, dd, J = 8.3, 1.4 Hz), 6.96-6.92 (2H, m), 3.33-3.20 (6H, m), 2.95 (2H, s), 2.47 (3H, d, J = 0.9 Hz), 2.21 (3H, d, J = 0.9 Hz), 0.87-0.84 (2H, m), 0.64-0.61 (2H, m). LC-MS R.T. 1.50 min, m/z 495 (M+1).
30		^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, dd, J = 7.8, 1.8 Hz), 7.41-7.33 (3H, m), 7.29-7.24 (1H, m), 7.14 (1H, dd, J = 8.3, 1.4 Hz), 6.52-6.49 (2H, m), 4.01 (4H, s), 3.58 (4H, s), 3.01 (1H, d, J = 9.6 Hz), 2.96 (3H, d, J = 9.6 Hz), 2.46 (3H, d, J = 0.9 Hz), 2.20 (3H, d, J = 0.9 Hz). LC-MS R.T. 1.35 min, m/z 481 (M+1).

Ex	Structure	NMR, LCMS
31		^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, dd, J = 7.8, 1.4 Hz), 7.43-7.39 (1H, m), 7.35-7.27 (2H, m), 7.14 (1H, dd, J = 8.3, 0.9 Hz), 6.99-6.98 (1H, m), 6.95-6.92 (2H, m), 3.24-3.22 (4H, m), 3.04 (1H, d, J = 9.6 Hz), 2.99 (1H, d, J = 9.6 Hz), 2.83-2.80 (4H, m), 2.48 (3H, d, J = 0.9 Hz), 2.21 (3H, d, J = 0.9 Hz). LC-MS R.T. 1.42 min, m/z 468 (M+1).
32		^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, d, J = 7.8 Hz), 7.40-7.35 (1H, m), 7.30-7.25 (1H, m), 7.13-7.10 (1H, m), 7.05-7.02 (1H, m), 6.86-6.79 (2H, m), 3.28-3.25 (4H, m), 3.03 (2H, q, J = 9.6 Hz), 2.85-2.82 (4H, m), 2.48 (3H, s), 2.21 (3H, s), 2.09 (3H, s). LC-MS R.T. 1.49 min, m/z 483 (M+1).
33		^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, dd, J = 8.0, 1.5 Hz), 7.39-7.34 (1H, m), 7.27 (1H, dd, J = 7.8, 1.5 Hz), 7.12-7.08 (2H, m), 6.60-6.54 (2H, m), 6.72 (3H, s), 3.30-3.27 (4H, m), 3.04 (2H, q, J = 9.6 Hz), 2.86-2.84 (4H, m), 2.46 (3H, s), 2.20 (3H, s). LC-MS R.T. 1.53 min, m/z 499 (M+1).
34		^{1}H-NMR ($CDCl_3$) δ: 7.79 (1H, dd, J = 8.0, 1.5 Hz), 7.45-7.41 (1H, m), 7.32-7.28 (1H, m), 7.21-7.17 (3H, m), 6.99 (1H, t, J = 8.5 Hz), 3.21-3.18 (4H, m), 3.04 (2H, q, J = 9.6 Hz), 2.89-2.86 (4H, m), 2.48 (3H, s), 2.21 (3H, s).
35		^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, d, J = 7.8 Hz), 7.40 (3H, d, J = 8.0 Hz), 7.32-7.27 (3H, m), 7.17 (1H, d, J = 8.0 Hz), 3.13-2.99 (5H, m), 2.56-2.46 (5H, m), 2.21 (3H, s), 1.91-1.83 (4H, m). LC-MS R.T. 1.50 min, m/z 467 (M+1).

Ex	Structure	NMR, LCMS
36		^{1}H-NMR ($CDCl_3$) δ: 8.61 (1H, d, J = 2.2 Hz), 7.76 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 8.3 Hz), 7.41-7.38 (1H, m), 728 (1H, t, J = 7.0 Hz), 7.23 (1H d, J = 8.3 Hz) 7.17-7.15 (1H, m), 3.07 (2H, d, J = 11.5 Hz), 2.97 (2H, q, J = 9.7 Hz), 2.76-2.68 (1H, m), 2.52-2.44 (5H, m), 2.18 (3H, s), 1.98-1.86 (4H, m). LC-MS R.T. 1.20 min, m/z 468 (M+1).

Example 37. 1,2-dimethyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-3*H*-phenoxazin-3-one

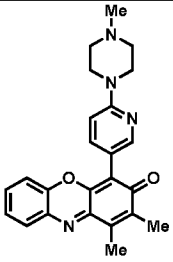
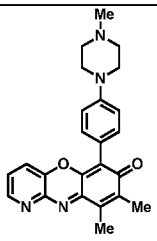
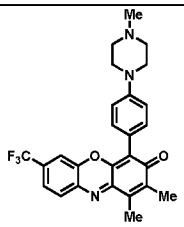
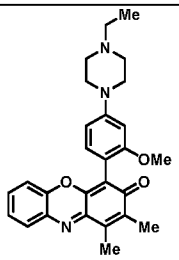


[00233] Example 5 (45 mg, 0.12 mmol), formaline (37%, 20 μL, 0.23 mmol), sodium triacetoxyborohydride (50 mg, 0.23 mmol) and acetic acid (14 mg, 0.23 mmol) were dissolved in dichloromethane (2 mL), and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was purified by amino silica gel column chromatography to afford the compound of Example 37 (19 mg, 41%).

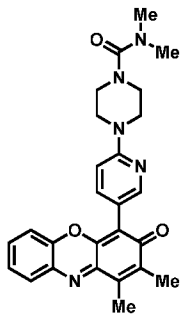
^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, d, J = 8.0 Hz), 7.42-7.38 (2H, m), 7.31-7.27 (1H, m), 7.17-7.15 (1H, m), 6.98 (2H, d, J = 8.8 Hz), 3.46 (4H, brs), 2.85 (4H, brs), 2.54 (3H, s), 2.47 (3H, s), 2.21 (3H, s). LC-MS: R.T. 0.89 min, m/z 400 (M+1).

[00234] In accordance with the method described in Example 37, Examples 38 to 41 shown in the following table were obtained using the compound of corresponding examples and raw materials.

Table 11.

Example	Structure	NMR, LCMS
38		^{1}H-NMR ($CDCl_3$) δ: 8.36 (1H, d, J = 2 Hz), 7.77 (1H, dd, J = 7.8, 1.4 Hz), 7.64 (1H, dd, J = 8.7, 2.3 Hz), 7.43-7.39 (1H, m), 7.31-7.26 (1H, m), 7.20 (1H, dd, J = 8.3, 0.9 Hz), 6.73 (1H, d, J = 8.7 Hz), 3.64-3.62 (4H, m), 2.55-2.53 (4H, m), 2.47 (3H, d, J = 0.9 Hz), 2.35 (3H, s), 2.20 (3H, d, J = 0.9 Hz). LC-MS R.T. 0.73 min, m/z 401 (M+1).
39		^{1}H-NMR ($CDCl_3$) δ: 8.49 (1H, dd, J = 4.5, 1.6 Hz), 7.45 (1H, dd, J= 8.2, 1.7 Hz), 7.34-7.27 (3H, m), 6.93 (2H, dd, J = 7.0, 1.7 Hz), 3.27-3.24 (4H, m), 2.56-2.53 (4H, m), 2.48 (3H, s), 2.31 (3H, s), 2.18 (3H, s). LC-MS R.T. 0.62 min, m/z 401 (M+1).
40		^{1}H-NMR ($CDCl_3$) δ: 7.85 (1H, d, J = 8.3 Hz), 7.51-7.48 (1H, m), 7.40-7.35 (3H, m), 6.99 (2H, d, J = 9.0 Hz), 3.39-3.35 (4H, m), 2.73-2.66 (4H, m), 2.46 (3H, s), 2.43 (3H, s), 2.21 (3H, s). LC-MS R.T. 0.99 min, m/z 468 (M+1).
41		^{1}H-NMR ($CDCl_3$) δ: 7.70 (1H, dd, J = 7.8, 1.4 Hz), 7.34-7.29 (1H, m), 7.22-7.20 (1H, m), 7.05 (2H, d, J = 8.3 Hz) 6.56-6.51 (2H, m), 3.67 (3H, s), 3.29-3.27 (4H, m), 2.63-2.61 (4H, m), 2.48 (2H, q, J = 7.2 Hz), 2.41 (3H, s), 2.15 (3H, s), 1.11 (3H, t, J = 7.2 Hz). LC-MS R.T. 0.86 min, m/z 445 (M+1).

Example 42. 4-[5-(1,2-dimethyl-3-oxo-3H-phenoxazin-4-yl)pyridin-2-yl]-N,N-dimethylpiperazine-1-carboxamide



[00235] Example 8 (35 mg, 0.09 mmol), dimethylcarbamoyl chloride (19 mg, 0.18 mmol) and diisopropylethylamine (35 mg, 0.27 mmol) were dissolved in toluene (2 mL), and the reaction mixture was stirred for 4 h at 120°C. The reaction mixture was evaporated and purified by amino silica gel column chromatography to afford the compound of Example 42 (40 mg, 96%) ^{1}H-NMR ($CDCl_3$) δ: 8.37 (1H, d, J = 2.4 Hz), 7.78 (1H, d, J = 8.0 Hz), 765 (1H, dd, J = 8.8, 2.4 Hz), 7.44-7.39 (1H, m), 7.32-7.27 (1H, m), 7.21-7.19 (1H, m), 6.74 (1H, d, J = 8.8, Hz), 3.64-3.61 (4H, m), 3.39-3.36 (4H, m), 2.87 (6H, s), 2.47 (3H, s), 2.21 (3H, s). LC-MS: R.T. 0.98 min, m/z 459 (M+1).

Example 43. Biological Activity: Cell viability evaluation test using human dermal fibroblasts derived from Friedreich ataxia patient

[00236] The ability of compounds to rescue Friedreich ataxia patient-derived dermal fibroblasts stressed by addition of L-buthionine-(S,R)-sulfoximine (BSO) was tested.

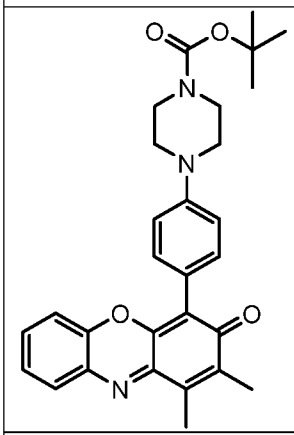
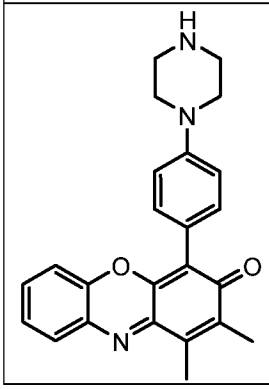
[00237] MEMα medium and Medium 199 medium were obtained from Thermo Scientific, and fetal bovine serum was obtained from DS Pharma. Basic fibroblast growth factor (b-FGF) was purchased from Funakoshi Co., Ltd. and epidermal growth factor (EGF) was purchased from PeproTech Inc. L-Buthionine-(S,R)-sulfoximine and bovine pancreas-derived insulin were purchased from Sigma. Calcein-AM was purchased from DOJINDO. Assay medium was a medium of 64% MEMα medium and 25% Medium 199 medium, and contains 10% fetal bovine serum, 10ng/ml of EGF, 10ng/ml of bFGF, and 10 μg/mL insulin. Cells were purchased from Coriell Institute.

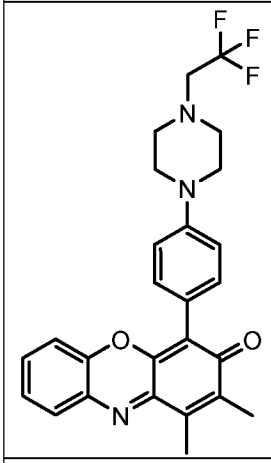
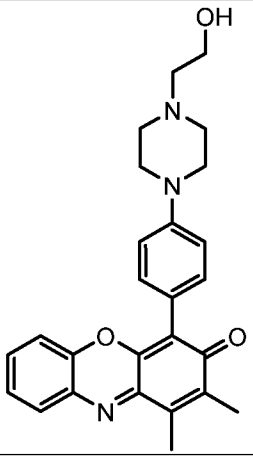
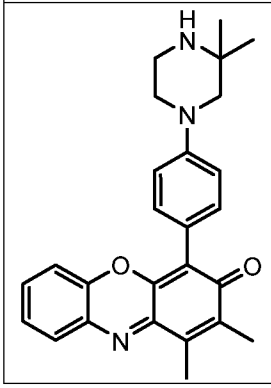
[00238] Test compounds were dissolved in DMSO to make a 1 mM or 10 mM stock solution. From this stock solution, serially diluted solutions were further prepared using DMSO and used in the assay.

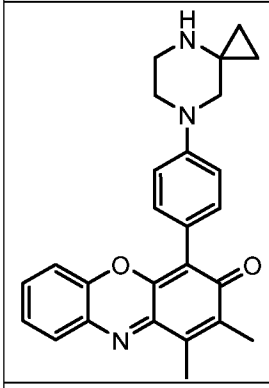
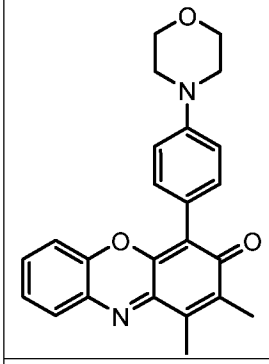
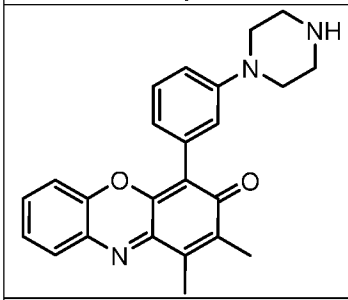
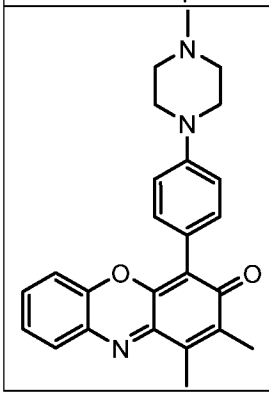
[00239] Friedreich ataxia patient-derived human dermal fibroblasts were suspended in assay medium, seeded into a 384-well plate at 650 cells/well/20 μl, and incubated at 37°C in a 5% carbon dioxide incubator overnight. A test compound solution prepared in assay medium from the serially diluted solution (DMSO) to be 5 times higher than the final concentration was added in 10 μL per well of the cell-seeded plate. Then, 10 μL of 150 μM BSO solution was added. The amount of reaction solution was adjusted to be finally 50 μL, and the final BSO concentration was 30 μM. The plate was incubated at 37°C in 5% CO2 for 48 hours, and then media were removed from all wells, and 20 μl of a Calcein-AM solution, which had

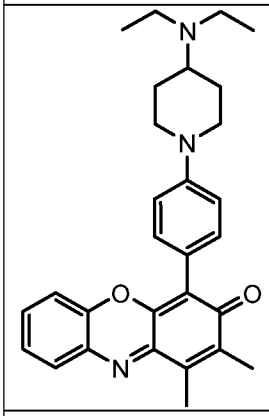
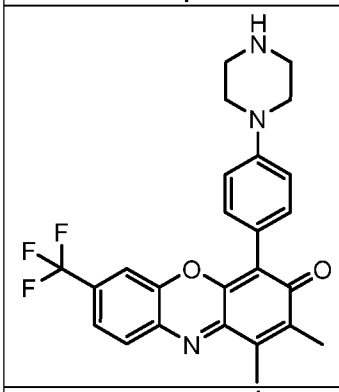
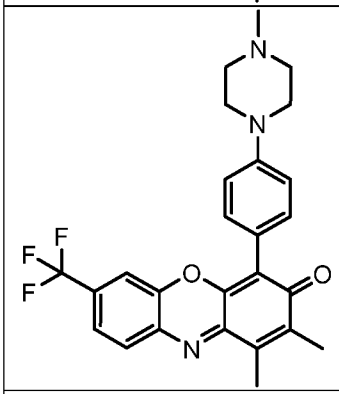
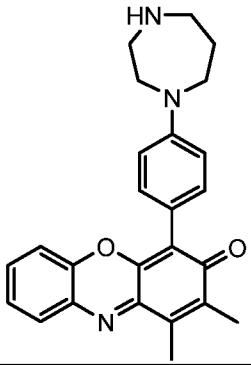
been 550-fold diluted by PBS, was added to each well. The plate was incubated at 37°C for 20 to 30 minutes, and then fluorescence (485 nm/525 nm of excitation/radiation wavelength) was measured by a fluorescence plate reader.

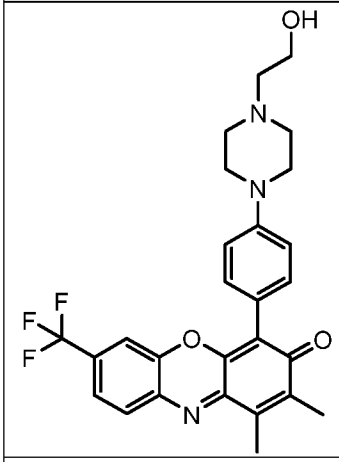
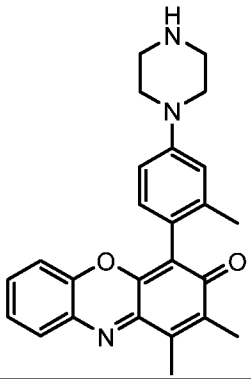
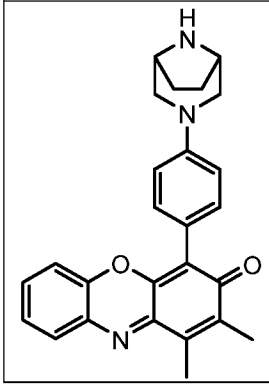
[00240] The degree of the viability of fibroblasts that were not treated with BSO was regarded as 100%, the degree of the viability of cells that were treated with BSO only (without a compound) was regarded as 0%, and the viability of cells that were treated with a compound was calculated.

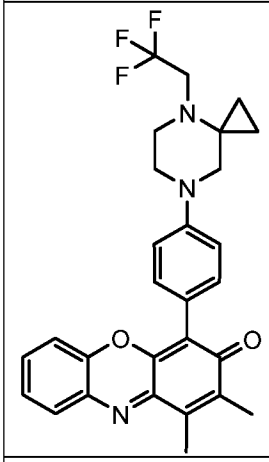
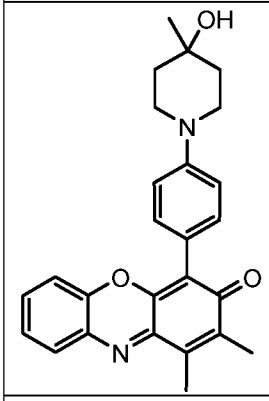
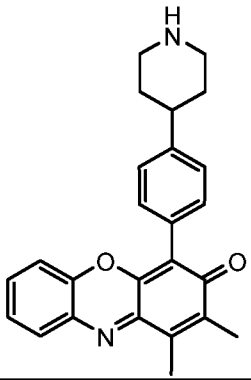
Compound	**EC_{50} (nM)**
	2.8
	0.4

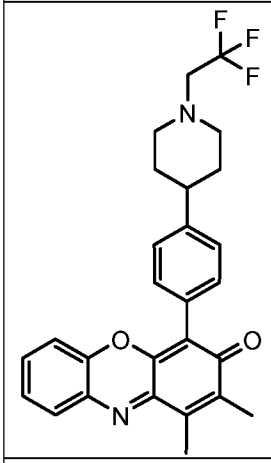
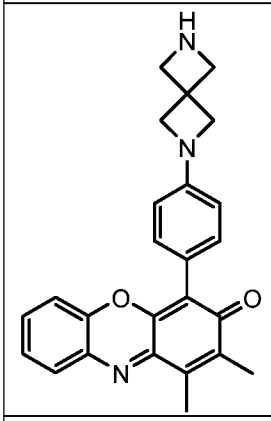
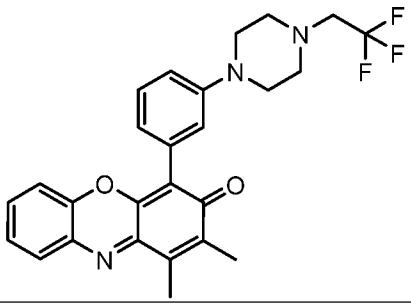
Compound	EC_{50} (nM)
	<3
	0.8
	0.8

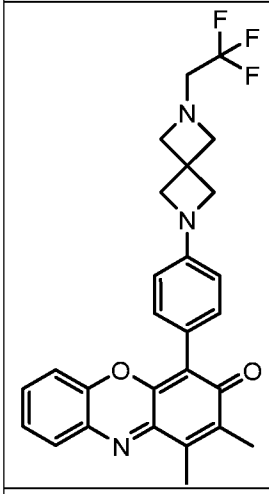
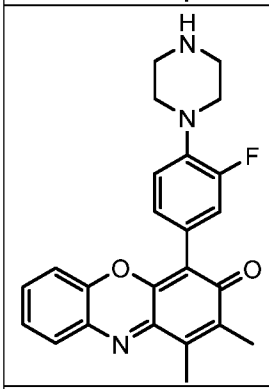
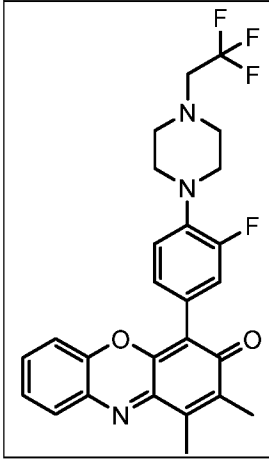
Compound	EC_{50} (nM)
	1.1
	0.9
	0.9
	0.9

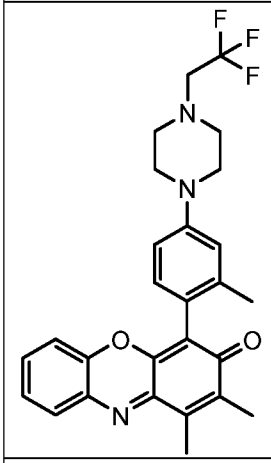
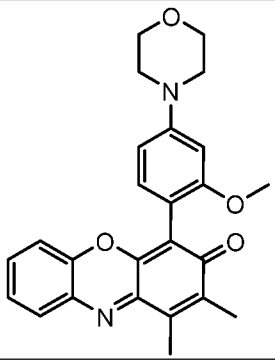
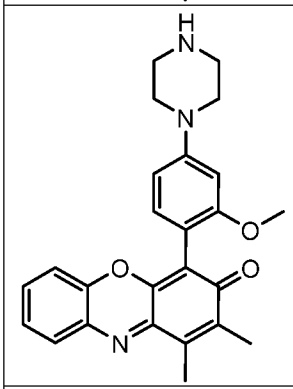
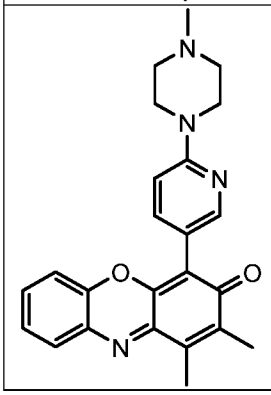
Compound	EC_{50} (nM)
	0.5
	0.5
	0.5
	0.9

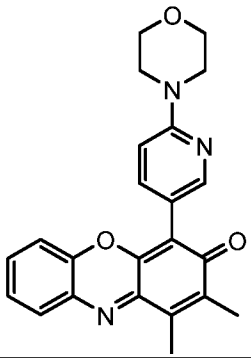
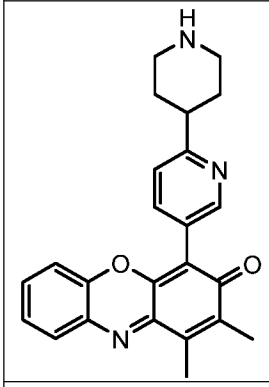
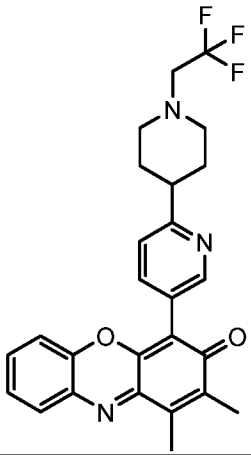
Compound	EC_{50} (nM)
	0.9
	0.9
	1

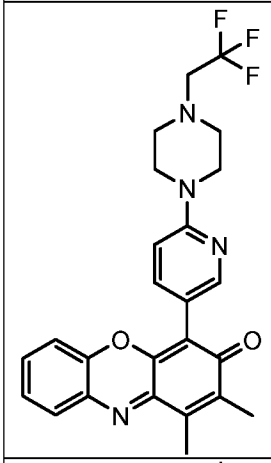
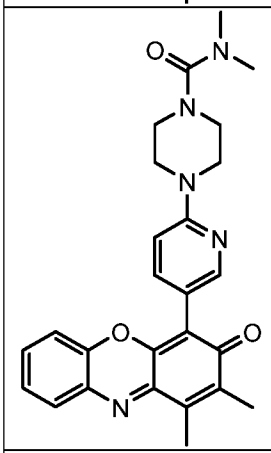
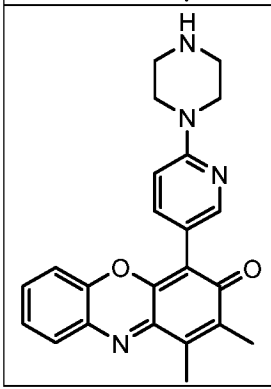
Compound	EC_{50} (nM)
	2.2
	1.8
	0.9

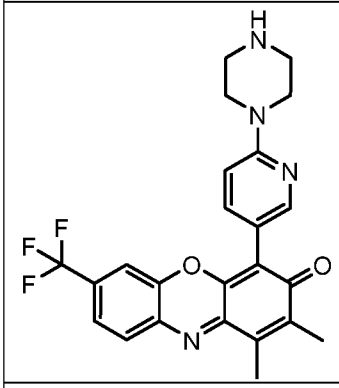
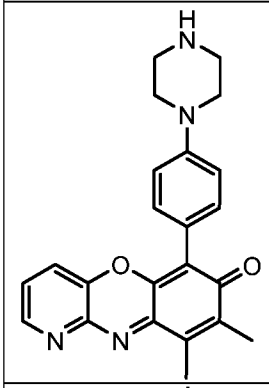
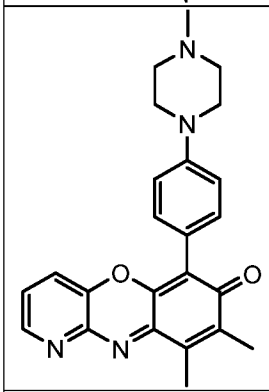
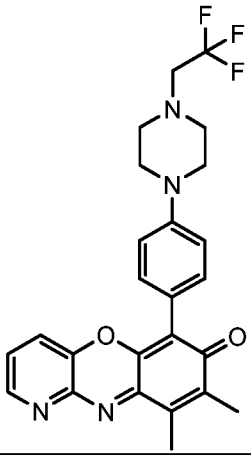
Compound	EC_{50} (nM)
	1.7
	1.6
	3.1

Compound	EC_{50} (nM)
	1.9
	1.0
	1.9

Compound	EC_{50} (nM)
	2.8
	0.5
	1.8
	0.5

Compound	EC_{50} (nM)
	0.9
	0.4
	0.9

Compound	EC_{50} (nM)
	1.7
	2.2
	0.9

Compound	EC_{50} (nM)
	0.8
	1.7
	1.7
	1.7

Example 44. Screening Compounds Described Herein in Fibroblasts from Huntington's Patients

[00241] Compounds described herein are tested using a screen similar to the one described in Example 43, and substituting FRDA cells with Huntington's cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number GM 04281). The compounds are tested for their ability to rescue human dermal fibroblasts from Huntington's patients from oxidative stress.

Example 45. Screening Compounds Described Herein in Fibroblasts from Leber's Hereditary Optic Neuropathy Patients

[00242] Compounds described herein are tested using a screen similar to the one described in Example 43, and substituting FRDA cells with Leber's Hereditary Optic Neuropathy (LHON) cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number GM03858). The compounds are tested for their ability to rescue human dermal fibroblasts from LHON patients from oxidative stress.

Example 46. Screening Compounds Described Herein in Fibroblasts from Parkinson's Disease Patients

[00243] Compounds described herein are tested using a screen similar to the one described in Example 43, and substituting FRDA cells with Parkinson's Disease (PD) cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number AG20439). The compounds are tested for their ability to rescue human dermal fibroblasts from Parkinson's Disease patients from oxidative stress.

Example 47. Screening Compounds Described Herein in Fibroblasts from CoQ10 Deficient Patients

[00244] Compounds described herein are tested using a screen similar to the one described in Example 43, and substituting FRDA cells with cells obtained from CoQ10 deficient patients harboring a CoQ2 mutation. The compounds are tested for their ability to rescue human dermal fibroblasts from CoQ10 deficient patients from oxidative stress.

Example 48. Screening Compounds Described Herein in Fibroblasts from Patients

[00245] Compounds described herein are tested using a screen similar to the one described in Example 43, and substituting FRDA cells with cells obtained from patients having an oxidative stress disorder described herein (e.g. MERRF, MELAS, Leigh Disease, KSS, Alzheimer's disease, ALS, a pervasive development disorder (such as autism, Rett's)). The compounds are tested for their ability to rescue human dermal fibroblasts from these patients from oxidative stress.

Example 49. Administration of compounds disclosed herein

[00246] A compound disclosed herein is presented in a capsule containing 300 mg of compound in a pharmaceutically acceptable carrier. A capsule is taken orally, once a day, preferably during breakfast or lunch. In case of very young children, the capsule is broken and its contents mixed with food.

Example 50. Protection Against APAP- or BSO-Induced Oxidative Stress in Liver

[00247] The testing, described below, induces oxidative stress in liver cells using an overdose of acetaminophen (APAP) or buthionine sulfoximine (BSO). Typical treatment for elevated liver enzymes or lysates is administration of N-Acetylcysteine (NAC). As shown in the figures, administration of a compound described herein (Compound A) resulted in a superior suppression of biomarkers of liver damage in comparison to the administration of NAC. The Compound A suppression of liver damage biomarkers appeared in a dose responsive manner for Study 1 and 2, although an intermediate dosing level in Study 3 indicated better results for liver enzyme levels. In addition, recovery of glutathione and isoprostane/creatinine levels were also demonstrated for Compound A.

Example 50A. Assessment of Enzyme and Lysate Concentration in Response to APAP Induced Liver Damage

[00248] A compound described herein (Compound A) was tested to determine its effects on liver enzymes and lysate concentrations following introduction of Acetaminophen (APAP) in sufficient quantity to cause liver trauma.

Experimental Design

[00249] Male C57BL/6 mice (CLEA Japan, Inc.), aged 10-12 weeks, were randomly and prospectively assigned to receive treatment with either a test compound (Compound A),

NAC, or vehicle only. The mice were challenged with 450 mg/kg body weight with acetaminophen (APAP) or an equal volume of the dosing vehicle (prepared in 0.9% sterile saline) via intraperitoneal injection.

Animal Housing and Environment

[00250] The animals were housed in disposable cages with sterile wood chip bedding, food, and water. The mice were acclimated for at least 3 days and given food and tap water *ad libitum*. The animals were examined prior to initiation of the study to assure adequate health and suitability. Animals that were found to be diseased or unsuitable were not assigned to the study.

[00251] During the course of the study, 12-hour light/12-hour dark cycles were maintained. A nominal temperature range of 20-23 °C with a relative humidity between 30% and 70% were also maintained. LabDiet 5053-certified PicoLab Rodent Diet and sterile water were provided *ad libitum*.

Test Article Administration

[00252] The animals were each administered with a single intraperitoneal injection 450 mg/kg body weight dose of APAP or vehicle only. All animals were dosed at approximately the same time on the dosing day (± 1 hour). Animals received either APAP only, vehicle only, APAP + Compound A, or APAP + NAC as described herein. The protective activity of the test article was assessed by administering Compound A (formulated in 0.5% methylcellulose) via oral gavage thirty minutes prior to APAP injection. The protective activity of NAC was assessed by administering NAC via oral gavage thirty minutes prior to APAP injection.

[00253] Liver injury and lipid peroxidation were assessed four hours after APAP administration by quantification of transaminase (alanine transaminase (ALT), aspartate amino transferase (AST)) enzyme activity in plasma and 4-hydroxynonenal (4-HNE) in liver lysates by ELISA. 4-HNE was normalized to input protein concentrations.

Test Summary

[00254] Figure 1 displays Study 1 four hour serum measurements for liver enzyme AST, for the control (Vehicle), APAP, APAP + Compound A (at 1 mg/kg and 10 mg/kg), and APAP + NAC (at 600mg/kg). Figure 2 displays Study 2 four hour serum measurements for liver enzyme AST, for the control (Vehicle), APAP, and APAP + Compound A (at 10 mg/kg).

[00255] Note the dose responsive drop in measured AST levels for Compound A administration in Figures 1 and 2, as compared with the standard of care treatment of NAC. At the 10 mg/kg dosing level for Compound A the reduction of AST serum levels is considerably lower than that provided by NAC, and approaches the control group (Vehicle) in Figure 1. Figure 2 confirms the measured AST reduction at the 10 mg/kg dosing level.

[00256] Figures 3 and 4 show the 4 hour serum measurements for enzyme ALT, for Study 1 and 2, respectively, for the same dosing as presented in Figures 1 and 2, respectively. ALT enzyme levels were dramatically reduced in a dose-dependent manner for Compound A, and the dose at 10 mg/kg provided a roughly equivalent drop to the drop provided by the standard of care treatment with NAC. Figure 4 confirms the measured ALT reduction at the 10 mg/kg dosing level.

[00257] Figure 5 displays the Study 1 results for lipid peroxidation marker 4-HNE. As seen in Figure 5, Compound A has a dose response drop in 4-HNE levels, where both 1 mg/kg and 10 mg/kg dosing levels exhibited superior results to the standard of care treatment using NAC. Figure 6 displays the Study 2 results (10 mg/kg dosing of Compound A) which confirm the reduction of 4-HNE levels, with levels even closer to the control (Vehicle).

[00258] Study 3 results are displayed in Figures 7, 8, and 9 for AST, ALT, and 4-HNE, respectively. Compound A dosing levels were provided at 1, 3, and 10 mg/kg, and consequently a finer granularity was obtained for this test. For the AST and ALT levels of Figures 7 and 8, respectively, the 3 mg/kg dosing level provided the largest reduction in enzyme levels. Figure 9 displays 4-HNE results with roughly equivalent reductions from all three dosing levels of 1, 3, and 10 mg/kg. The results of Figure 9 are consistent with Figure 5 where 1 and 10 mg/kg dosing levels exhibited similar reductions of 4-HNE levels.

[00259] Additional indicators for liver damage and lipid peroxidation were provided by the GSH (Glutathione) level and Isoprostane/Creatinine ratios presented in Figures 10 and 11, respectively. Figure 10 results for Compound A again show a dose responsive recovery of GSH levels, dosing of 10 mg/kg showing better results than 1 mg/kg dosing, in excess of the recovery provided by the standard of care using NAC. Figure 11 exhibits a recovery closer to the control ratiofor dosing level of 10 mg/kg.

Example 50B. Assessment of Enzyme Concentration in Response to BSO Induced Liver Damage

[00260] Compound A was tested to determine its effects on liver enzymes concentrations following introduction of Buthionine Sulfoximine (BSO) in sufficient quantity to cause liver trauma.

Experimental Design

[00261] Male C57BL/6 mice (CLEA Japan, Inc.), aged 10-12 weeks, were randomly and prospectively assigned to receive treatment with either a test compound, or vehicle only. The mice were challenged with 1000 mg/kg body weight once daily for four days with BSO via intraperitoneal injection.

Animal Housing and Environment

[00262] Conditions were the same as provided in Example 50A.

Test Article Administration

[00263] The animals were each administered a single intraperitoneal injection of BSO or saline vehicle only at 1000 mg/kg body weight once per day for four days. Twenty four hours after the final BSO injection, plasma was prepared and quantification of AST and ALT enzyme acdfdtivity was performed. In conjunction with the administration of BSO, the test Compound A (or saline vehicle only) was administered by oral gavage twice per day over the same four days at dosing levels of 0.1, 1.0, and 10 mg/kg body weight.

Test Summary

[00264] Figure 12 displays AST enzyme levels and reduction in those levels in a dose responsive manner using Compound A, where "saline" in the figure indicates no oxidative stress challenge (no BSO) and "vehicle" indicates an oxidative stress challenge (BSO) but no test compound. Figure 13 shows similar dose responsive reductions in ALT enzyme levels, and for the 10 mg/kg dosing level a reduction approaching the level of the saline control group (no BSO or Compound A administered), where "saline" in the figure indicates no oxidative stress challenge (no BSO) and "vehicle" indicates an oxidative stress challenge (BSO) but no test compound.

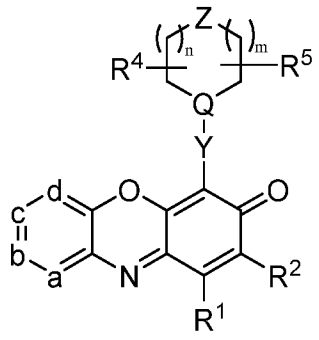
[00265] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

[00266] Although the foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

What is claimed is:

1. A compound of Formula I:



(Formula I)

or the reduced form thereof;

wherein:

R^1 and R^2 are independently selected from the group consisting of H and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl, and wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -C(O)OH, -$NR^{25}R^{26}$, -O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl;

a, b, c, and d are independently selected from the group consisting of -$C(R^3)$- and –N-, with the proviso that no more than three of a, b, c, and d are -N-;

each R^3 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -CN, -C(O)OH, -$NR^{27}R^{28}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{15}R^{16}$, -O-C(O)-O-C_1-C_6 alkyl, -C(O)$NR^{29}R^{30}$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{17}R^{18}$, -NHC(O)O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl, wherein each C_1-C_6 alkyl and -O-C_1-C_6 alkyl are independently optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -CN, -C(O)OH, -$NR^{31}R^{32}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{19}R^{20}$, -O-C(O)-O-C_1-C_6 alkyl, -$C(O)NH_2$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{21}R^{22}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl;

n and m are independently 0, 1, or 2;

Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-

membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -OH, -CN, -C(O)OH, -$NR^{33}R^{34}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -$S(O)_2$-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, and 3 to 8-membered saturated heterocyclyl;

R^4 and R^5 are independently selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -CN, -C(O)OH, -$NR^{35}R^{36}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl; or

R^4 and R^5 together with the intervening atom(s) form a 3-8 membered carbocylic or 3-8 membered heterocyclic ring, wherein the 3-8 membered carbocylic or 3-8 membered heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of –OH, -$NR^{37}R^{38}$, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and -O-C_1-C_6 alkyl;

Q is N or CH;

Z is –N(R^6)-, -C(R^7)(R^8)-, or –O-;

R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)R^9, -C(O)OR^{10}, -C(O)$NR^{11}R^{12}$, -$S(O)_2$-C_1-C_6 alkyl, or -$S(O)_2$-$NR^{23}R^{24}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -C(O)OH, -$NR^{39}R^{40}$, -O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, and 3 to 8-membered saturated heterocyclyl;

R^7 and R^8 are independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, and –$NR^{13}R^{14}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH, halogen, -C(O)OH, -NH_2, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl; or

R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 haloalkyl, halogen, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -OH, -C(O)OH, -NH_2, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, and -C(O)-heterocyclyl,;

R^9 is C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^{10} is H or C_1-C_6 alkyl;

R^{11} and R^{12} are independently selected from the group consisting of H, C_1-C_6 alkyl,

and C_1-C_6 haloalkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or

R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring; and

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, and R^{40} are independently selected from the group consisting of H and C_1-C_6 alkyl;

or a salt, deuterated form, solvate, hydrate, stereoisomer, or mixture of stereoisomers thereof.

2. The compound of claim 1, wherein each R^3 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -C(O)OH, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -C(O)$NR^{29}R^{30}$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{17}R^{18}$, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl, wherein each C_1-C_6 alkyl is independently optionally substituted with one or more substituents independently selected from the group consisting of: -OH, -CN, -C(O)OH, -$NR^{31}R^{32}$, -C(O)-C_1-C_6 alkyl, -C(O)-aryl, -C(O)-heterocyclyl, -O-C(O)-$NR^{19}R^{20}$, -O-C(O)-O-C_1-C_6 alkyl, -$C(O)NH_2$, -$S(O)_2$-C_1-C_6 alkyl, -$S(O)_2$-$NR^{21}R^{22}$, -NHC(O)O-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3 to 8-membered saturated heterocyclyl, and C_6-C_{10} aryl.

3. The compound of any one of claims 1-2, wherein:

R^1 and R^2 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl;

each R^3 is independently selected from the group consisting of H, halogen, unsubstituted C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl;

R^4 and R^5 are independently selected from the group consisting of H and

unsubstituted C_1-C_6 alkyl; or

R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocylic or 3-8 membered unsubstituted heterocyclic ring;

R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OR^{10}, or -C(O)$NR^{11}R^{12}$, wherein the C_1-C_6 alkyl is optionally substituted with one or more –OH;

R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and –$NR^{13}R^{14}$; or

R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 haloalkyl, halogen, and C_1-C_6 alkyl;

R^{11} and R^{12} are independently selected from the group consisting of H and C_1-C_6 alkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring; and

R^{13} and R^{14} are independently selected from the group consisting of H and C_1-C_6 alkyl; or

R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring.

4. The compound of any one of claims 1-3, wherein:

R^1 and R^2 are independently unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl;

each R^3 is independently selected from the group consisting of H and C_1-C_6 haloalkyl;

Y is 6-membered aryl or 6-membered heteroaryl, wherein the 6-membered aryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl;

R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl; or

R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocylic or 3-8 membered unsubstituted heterocyclic ring;

R^6 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OR^{10}, or -C(O)$NR^{11}R^{12}$, wherein the C_1-

C_6 alkyl is optionally substituted with one or more –OH;

R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and $–NR^{13}R^{14}$; or

R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from C_1-C_6 haloalkyl;

R^{10} is C_1-C_6 alkyl;

R^{11} and R^{12} are independently C_1-C_6 alkyl; and

R^{13} and R^{14} are independently C_1-C_6 alkyl.

5. The compound of claim 1, wherein Y is unsubstituted pyridyl or Y is phenyl, optionally substituted with one or more independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl; R^1 and R^2 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is a linear or branched chain alkyl; each R^4 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, wherein the "C_1-C_6 alkyl" is optionally substituted with one or more -OH; and R^5 is selected from the group consisting of H, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected from the group consisting of: -OH and halogen.

6. The compound of any one of claims 1 or 2, wherein R^1 and R^2 are independently H or unsubstituted C_1 alkyl.

7. The compound of any one of claims 1, 2, or 6, wherein R^1 and R^2 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl.

8. The compound of any one of claims 1-5, wherein R^1 and R^2 are independently unsubstituted C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is a linear or branched chain alkyl.

9. The compound of any one of claims 1-8, wherein R^1 and R^2 are methyl.

10. The compound of any one of claims 1-9, wherein a, b, c, and d are -C(R^3)-.

11. The compound of any one of claims 1-9, wherein b, c, and d are -C(R^3)-, and wherein a is –N-.

12. The compound of any one of claims 1-11, wherein each R^3 is H.

13. The compound of any one of claims 1-11, wherein b and d are -CH-, and wherein c is –C(CF_3)-.

14. The compound of any one of claims 1-13, wherein n and m are 1.

15. The compound of any one of claims 1-13, wherein n and m are 0.

16. The compound of any one of claims 1-13, wherein one of n and m is 1, and the other of n and m is 2.

17. The compound of any one of claims 1-16, wherein Y is phenyl substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, and -O-C_1-C_6 alkyl.

18. The compound of any one of claims 1-17, wherein Y is phenyl substituted with one or more substituents independently selected from C_1-C_6 alkyl.

19. The compound of any one of claims 1-18, wherein Y is phenyl substituted with one unsubstituted C_1 alkyl.

20. The compound of any one of claims 1-16, wherein Y is unsubstituted phenyl.

21. The compound of any one of claims 1-16, wherein Y is unsubstituted pyridyl.

22. The compound of any one of claims 1-21, wherein R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_6 alkyl.

23. The compound of any one of claims 1-22, wherein R^4 and R^5 are H.

24. The compound of any one of claims 1-21, wherein R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted carbocyclic ring.

25. The compound of any one of claims 1-21, wherein R^4 and R^5 together with the intervening atom(s) form a 3-8 membered unsubstituted heterocyclic ring.

26. The compound of any one of claims 1-25, wherein Q is N.

27. The compound of any one of claims 1-25, wherein Q is CH.

28. The compound of any one of claims 1-27, wherein Z is $-N(R^6)-$.

29. The compound of any one of claims 1-27, wherein Z is $-C(R^7)(R^8)-$.

30. The compound of any one of claims 1-27, wherein Z is -O-.

31. The compound of any one of claims 1-28, wherein R^6 is H.

32. The compound of any one of claims 1-28, wherein R^6 is C_1-C_6 alkyl substituted with one or more -OH.

33. The compound of any one of claims 1-28, wherein R^6 is unsubstituted C_1-C_6 alkyl.

34. The compound of any one of claims 1-28, wherein R^6 is C_1-C_6 haloalkyl.

35. The compound of any one of claims 1-28, wherein R^6 is $-C(O)OR_{10}$.

36. The compound of any one of claims 1-28, wherein R^6 is $-C(O)NR_{11}R_{12}$.

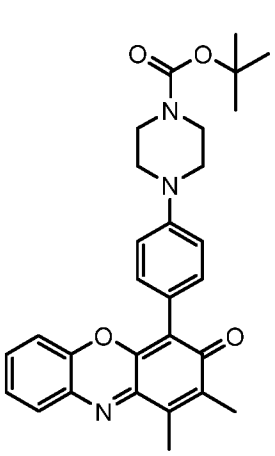
37. The compound of any one of claims 1-27 or 29, wherein R^7 and R^8 are independently selected from the group consisting of H, -OH, unsubstituted C_1-C_6 alkyl, and $-NR^{13}R^{14}$.

38. The compound of any one of claims 1-27 or 29, wherein R^7 and R^8 together with the carbon atom to which they are attached form a 4-8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from C_1-C_6 haloalkyl.

39. The compound of any one of claims 1-11, wherein R^4 and R^5 are independently selected from the group consisting of H and unsubstituted C_1-C_3 alkyl.

40. The compound of any one of claims 1-11, wherein R^4 and R^5 are the same and selected from the group consisting of H and unsubstituted C_1 alkyl.

41. The compound of claim 1, selected from the group consisting of: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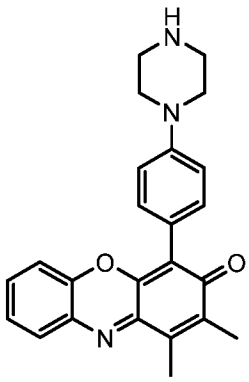
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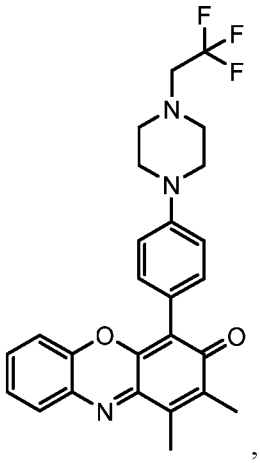
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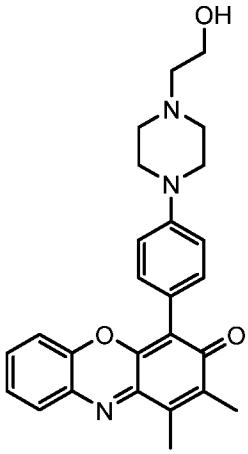
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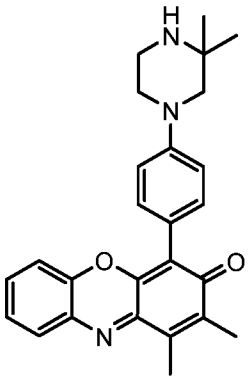
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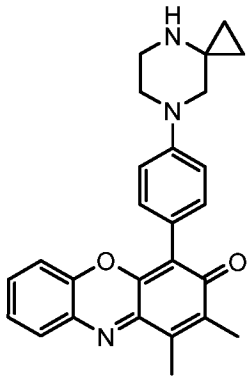
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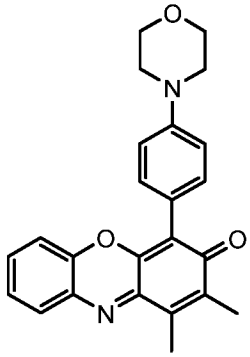
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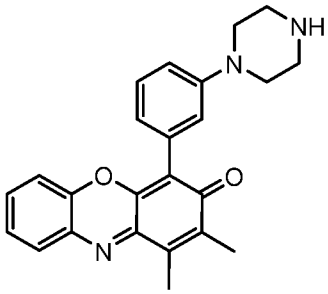
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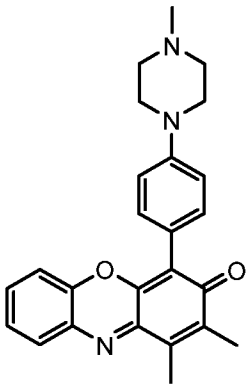
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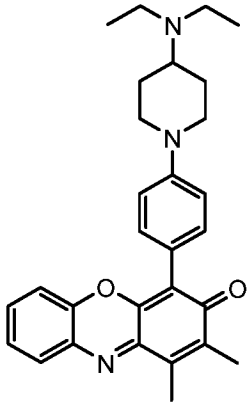
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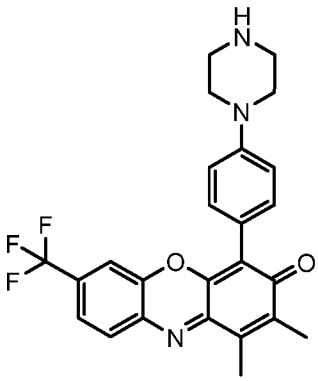
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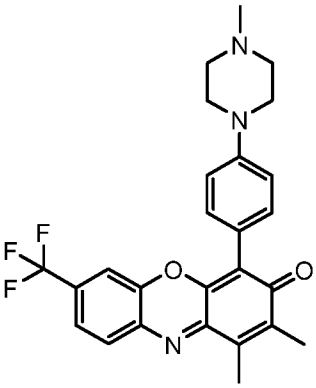
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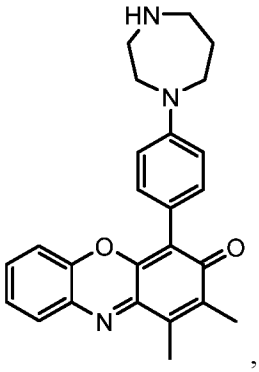
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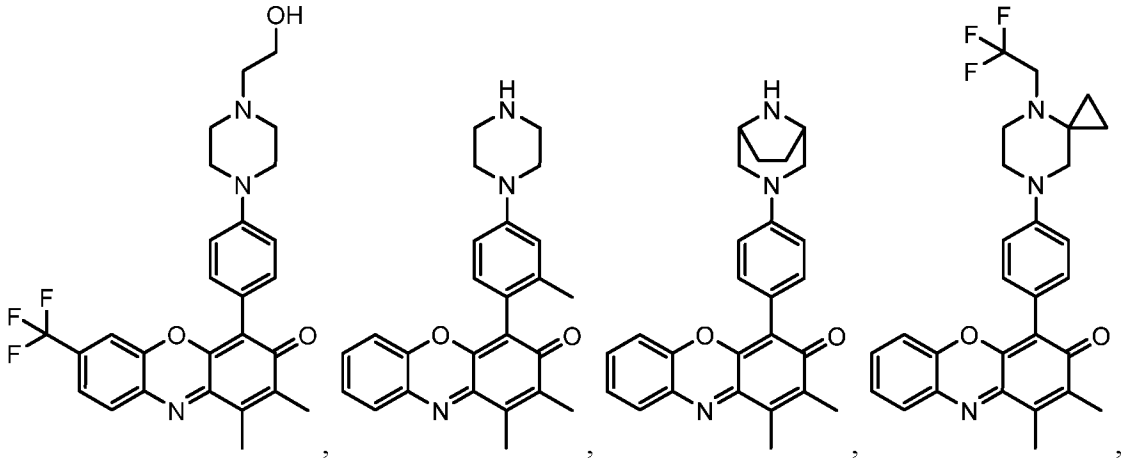

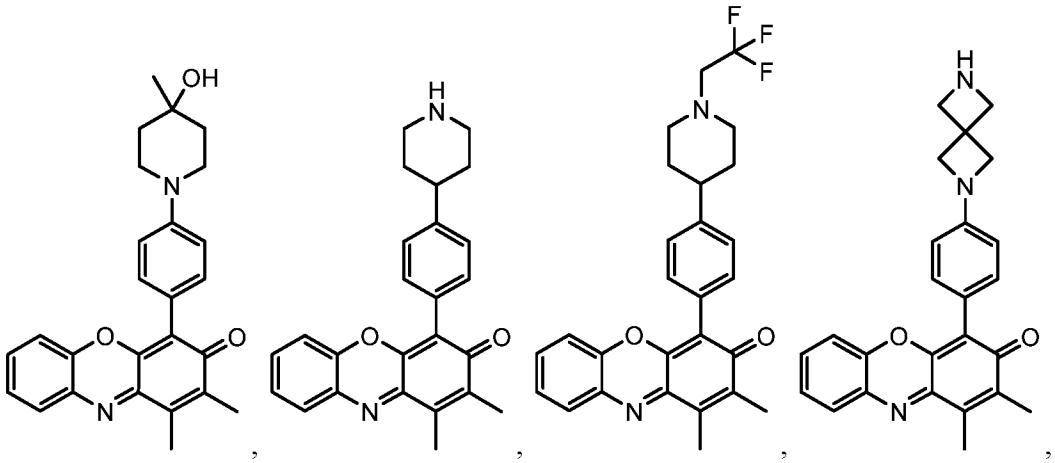

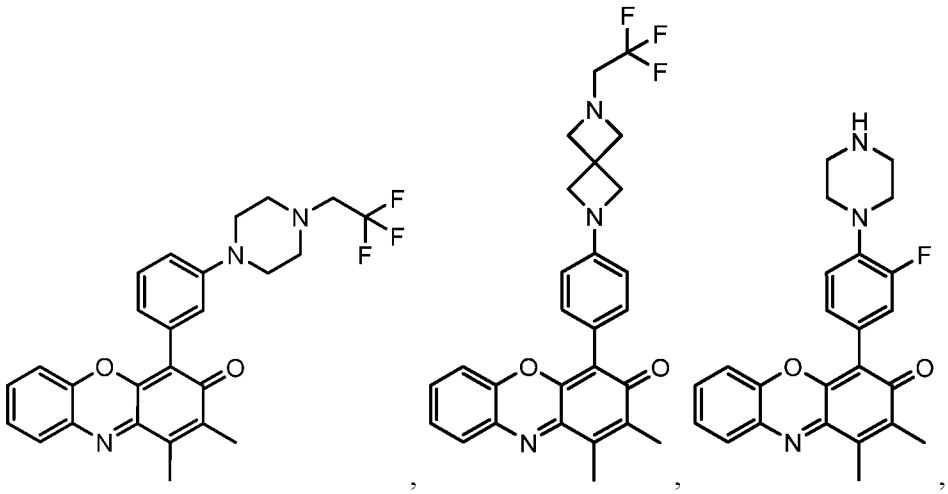

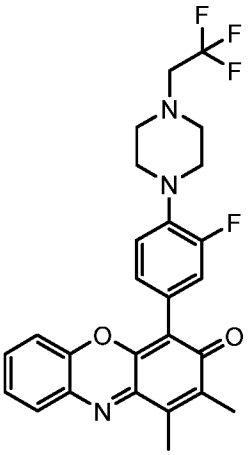
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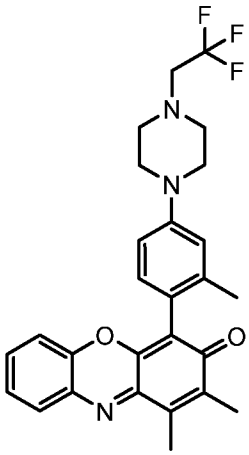
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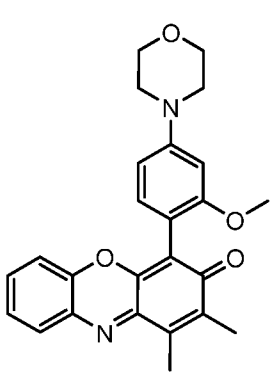
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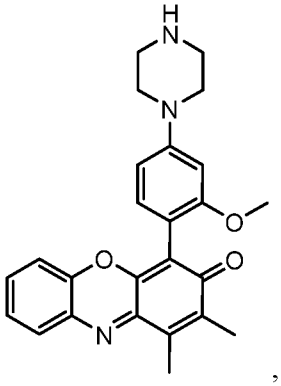
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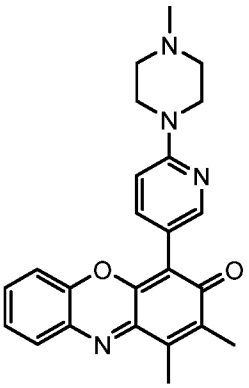
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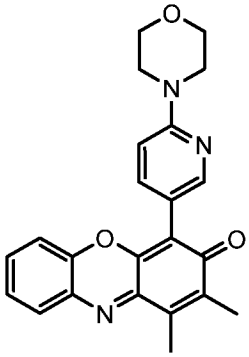
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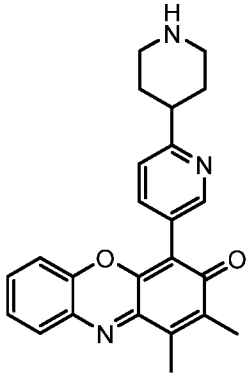
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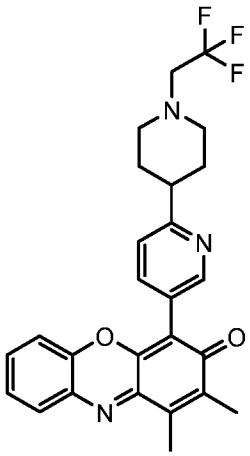
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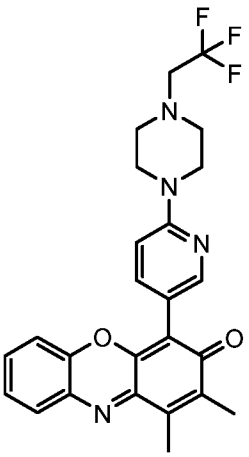
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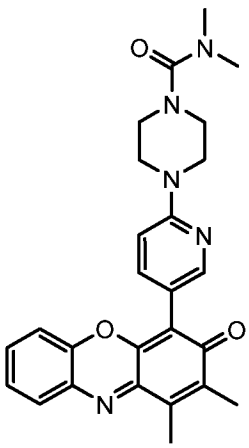
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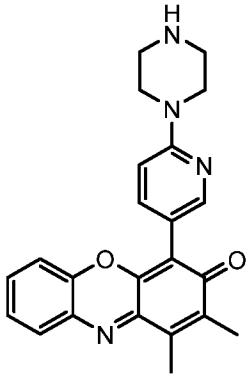
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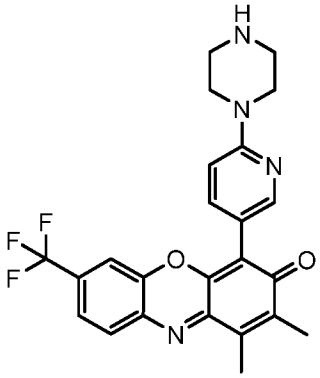
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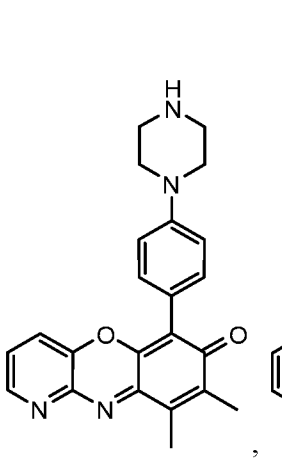
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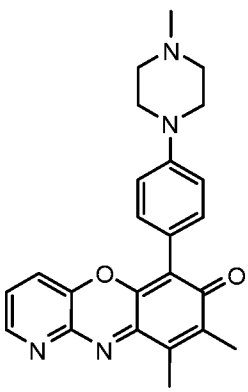
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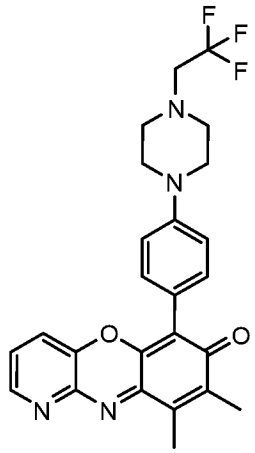
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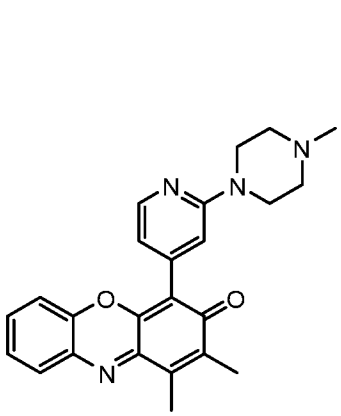
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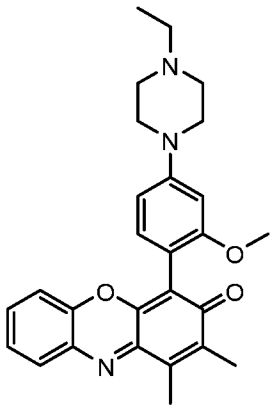
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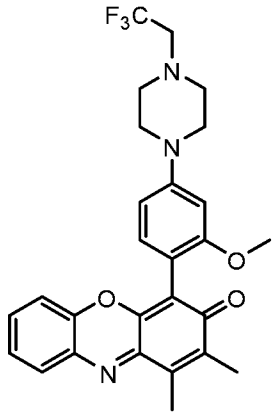
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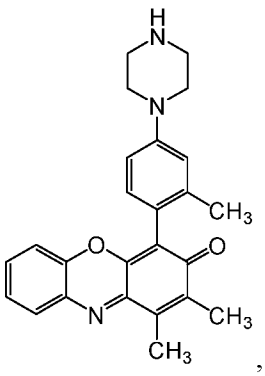
or the reduced form thereof;

or a salt, deuterated form, solvate, hydrate, stereoisomer, or mixture of stereoisomers thereof.

42. The compound of claim 1, wherein the compound is selected from the group consisting of: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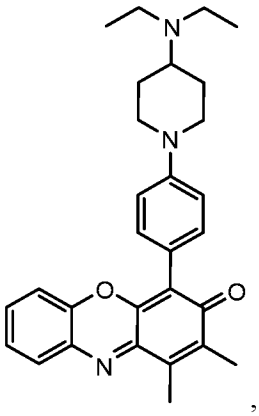
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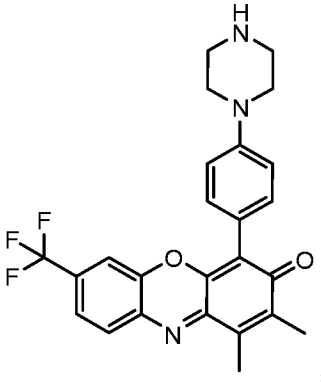
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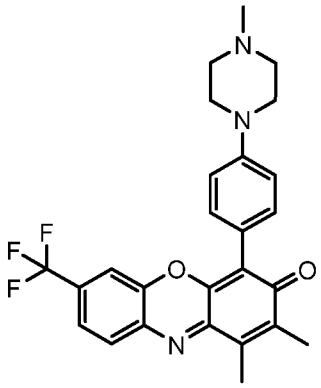
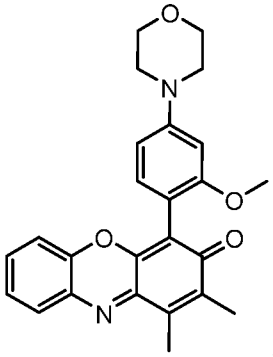
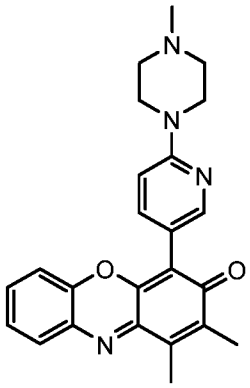
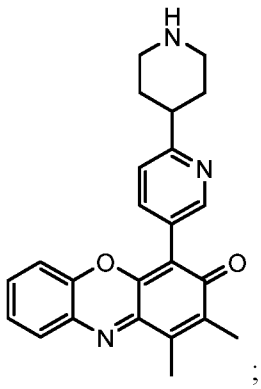

, 
, 
, and 
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or the reduced form thereof;

or a salt, deuterated form, solvate, or hydrate thereof.

43. The compound of any one of claims 1-42, wherein the compound is in the oxidized form.

44. The compound of any one of claims 1-42, wherein the compound is in the reduced form.

45. The compound of any one of claims 1-44, wherein the compound is not a salt.

46. The compound of any one of claims 1-44, wherein the compound is a pharmaceutically acceptable salt.

47. A pharmaceutical composition comprising a compound of any one of claims 1-46 and a pharmaceutically acceptable carrier.

48. The pharmaceutical composition of claim 47, further comprising an additional agent selected from the group consisting of omega-3 fatty acids, CoQ10, and N-acetyl cysteine (NAC).

49. The pharmaceutical composition of claim 47 or 48, wherein the additional agent is selected from the group consisting of docosahexaenoic acid, eicosapentaenoic acid, CoQ10, and n-acetyl cysteine.

50. The pharmaceutical composition of any one of claims 47-49, wherein the additional agent has a weight % concentration of 1-99% based on the total weight of the compound and the additional agent.

51. A method of treating or suppressing an oxidative stress disorder, treating or suppressing a liver or kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, comprising administering to a subject in need thereof a therapeutically effective amount, a prophylactically effective amount, or effective amount of a compound according to any one of claims 1-46, or a pharmaceutical composition of claim 47-50, wherein when the compound is a salt, the salt is a pharmaceutically acceptable salt.

52. The method of claim 51, wherein the method is a method of treating or suppressing an oxidative stress disorder selected from the group consisting of: a mitochondrial disorder; an inherited mitochondrial disease; Alpers Disease; Barth syndrome; a Beta-oxidation Defect; Carnitine-Acyl-Carnitine Deficiency; Carnitine Deficiency; a Creatine Deficiency Syndrome; Co-Enzyme Q10 Deficiency; Complex I Deficiency; Complex II Deficiency; Complex III Deficiency; Complex IV Deficiency; Complex V Deficiency; COX Deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I Deficiency; CPT II deficiency; Friedreich's Ataxia (FA); Glutaric Aciduria Type II; Kearns-Sayre Syndrome (KSS); Lactic Acidosis; Long-Chain Acyl-CoA Dehydrongenase Deficiency (LCAD); LCHAD; Leigh Syndrome; Leigh-like Syndrome; Leber's Hereditary Optic Neuropathy (LHON); Lethal Infantile Cardiomyopathy (LIC); Luft Disease; Multiple Acyl-

CoA Dehydrogenase Deficiency (MAD); Medium-Chain Acyl-CoA Dehydrongenase Deficiency (MCAD); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS); Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Recessive Ataxia Syndrome (MIRAS); Mitochondrial Cytopathy, Mitochondrial DNA Depletion; Mitochondrial Encephalopathy; Mitochondrial Myopathy; Myoneurogastointestinal Disorder and Encephalopathy (MNGIE); Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP); Pearson Syndrome; Pyruvate Carboxylase Deficiency; Pyruvate Dehydrogenase Deficiency; a POLG Mutation; a Respiratory Chain Disorder; Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD); SCHAD; Very Long-Chain Acyl-CoA Dehydrongenase Deficiency (VLCAD); a myopathy; cardiomyopathy; encephalomyopathy; a neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); a motor neuron disease; a neurological disease; epilepsy; an age-associated disease; macular degeneration; diabetes; metabolic syndrome; a genetic disease; Huntington's Disease; a mood disorder; schizophrenia; bipolar disorder; a pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett's disorder; PDD-not otherwise specified (PDD-NOS); a cerebrovascular accident; stroke; a vision impairment; optic neuropathy; dominant inherited juvenile optic atrophy; optic neuropathy caused by a toxic agent; glaucoma; Stargardt's macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemic reperfusion related retinal injury; oxygen poisoning; a haemoglobionopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit/hyperactivity disorder (ADHD); a neurodegenerative disorder resulting in hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally inherited diabetes and deafness (MIDD); chronic fatigue; contrast-induced kidney damage; contrast-induced retinopathy damage; Abetalipoproteinemia; retinitis pigmentosum; Wolfram's disease; Tourette syndrome; cobalamin c defect; methylmalonic aciduria; glioblastoma; Down's syndrome; acute tubular necrosis; a muscular dystrophy; a leukodystrophy; Progressive Supranuclear Palsy; spinal muscular atrophy; hearing loss; noise induced hearing loss; traumatic brain injury; Juvenile Huntington's Disease; Multiple Sclerosis; NGLY1; Multisystem atrophy; Adrenoleukodystrophy; and Adrenomyeloneuropathy.

53. The method of claim 51, wherein the method is for treating or suppressing a

liver disorder characterized by one or more inflammation and/or oxidative stress biomarkers.

54. The method of claim 53, wherein the liver disorder is selected from the group consisting of NAFL, NASH, alcoholic hepatitis, cholestatic liver disease, viral hepatitis, drug-induced liver toxicity, hemochromatosis, Wilson's disease, transplant reperfusion injury, and hepatic insufficiency.

55. The method of claim 54, wherein the hepatic insufficiency is caused by traumatic injury, systemic inflammatory response syndrome (SIRS), sepsis, and/or severe illness.

56. The method of claim 54, wherein the liver disorder is drug-induced liver toxicity.

57. The method of claim 51, wherein the method is for treating or suppressing a kidney disorder characterized by one or more inflammation and/or oxidative stress biomarkers.

58. The method of claim 57, wherein the kidney disorder is kidney insufficiency caused by traumatic injury and/or illness.

59. The method of any one of claims 51-58, wherein the method is for treating the disorder.

60. The method of any one of claims 51-58, wherein the method is for suppressing the disorder.

61. The method of any one of claims 51-60, wherein administering the compound is done orally.

62. The method of claim 61, wherein administering the compound is achieved in a medical food.

63. The method of claim 61, wherein administering the compound is achieved in an ingestible supplement.

64. The method of any one of claims 51-60, wherein administering the compound is done via injection.

65. The method of any one of claims 51-60, wherein administering the compound is done topically.

66. The method of any one of claims 51-65, wherein the subject is a human.

67. The method of claim 66, wherein the amount of the compound is about 0.5 mg/kg to about 10 mg/kg of body weight.

68. The method of claim 66, wherein the amount of the compound is about 1 mg/kg to about 8 mg/kg of body weight.

69. The method of claim 66, wherein the amount of the compound is about 1 mg/kg to about 5 mg/kg body weight.

70. The method of any one of claims 51-69 further comprising administering an additional agent wherein the additional agent is selected from the group consisting of omega-3 fatty acids, CoQ10, and N-acetyl cysteine (NAC).

71. The method of claim 70, wherein the additional agent is selected from the group consisting of NAC and DHA.

72. The method of claim 70 or 71, wherein the additional agent has a weight % concentration of 1-99% based on the total weight of the compound and the additional agent.

73. The method of claim 51, wherein the method is a method for modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or

more energy biomarkers, wherein the one or more energy biomarkers are selected from the group consisting of: lactic acid (lactate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; pyruvic acid (pyruvate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; lactate/pyruvate ratios, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized glutathione levels, or reduced/oxidized glutathione ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized cysteine levels, or reduced/oxidized cysteine ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; phosphocreatine levels, NADH (NADH + H^+) levels; NADPH (NADPH + H^+) levels; NAD levels; NADP levels; ATP levels; reduced coenzyme Q (CoQred) levels; oxidized coenzyme Q (CoQox) levels; total coenzyme Q (CoQtot) levels; oxidized cytochrome C levels; reduced cytochrome C levels; oxidized cytochrome C/reduced cytochrome C ratio; acetoacetate levels, b-hydroxy butyrate levels, acetoacetate/b-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; levels of reactive oxygen species; levels of oxygen consumption (VO2); levels of carbon dioxide output (VCO2); respiratory quotient (VCO2/VO2); exercise tolerance; and anaerobic threshold.

74. The method of any one of claims 51-65, wherein the subject is a eukaryotic system.

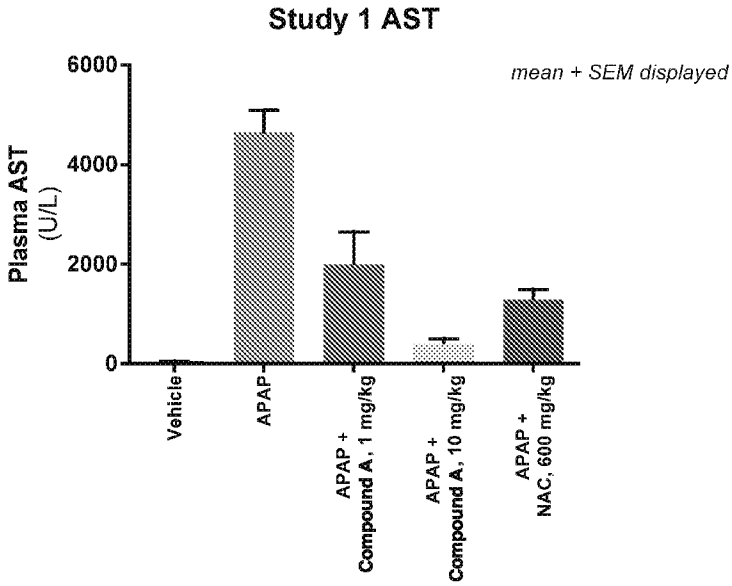
Study 1 AST
mean + SEM displayed
Plasma AST (U/L)
6000
4000
2000
0
Vehicle
APAP
APAP + Compound A, 1 mg/kg
APAP + Compound A, 10 mg/kg
APAP + NAC, 600 mg/kg

FIG. 1

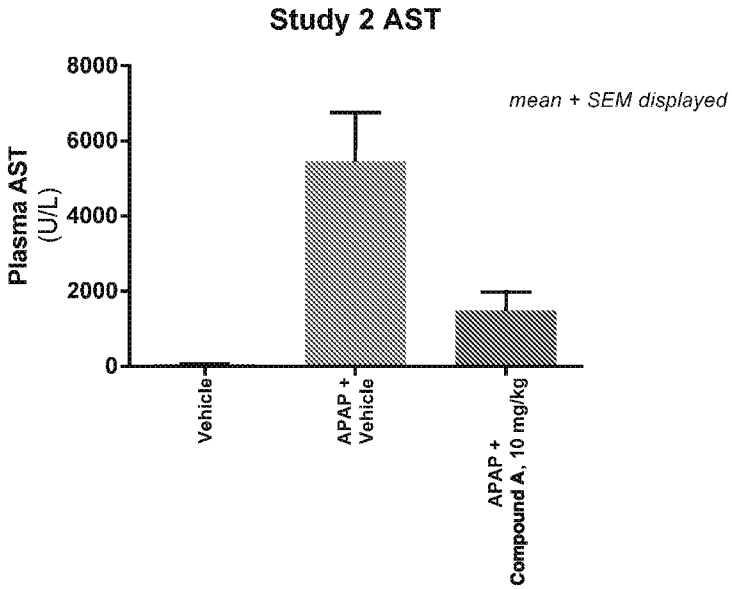
Study 2 AST
mean + SEM displayed
Plasma AST (U/L)
8000
6000
4000
2000
0
Vehicle
APAP + Vehicle
APAP + Compound A, 10 mg/kg

FIG. 2

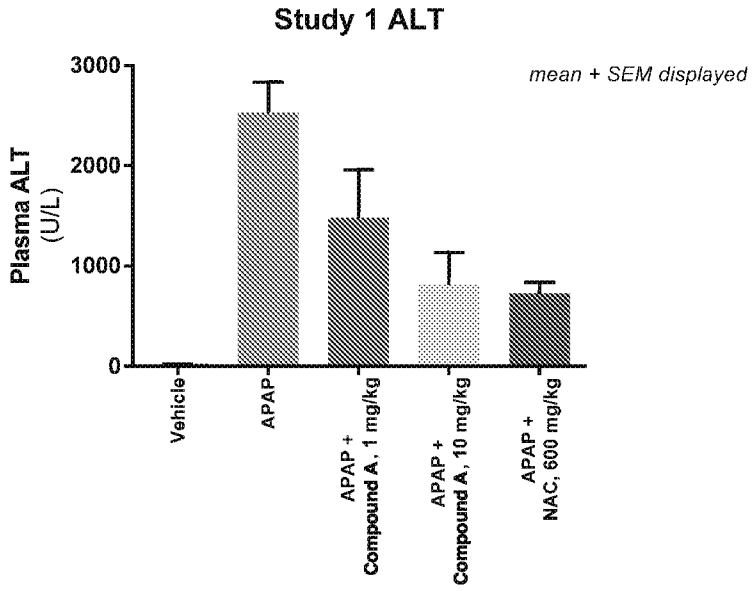
Study 1 ALT
mean + SEM displayed
Plasma ALT (U/L)
3000
2000
1000
0
Vehicle
APAP
APAP + Compound A, 1 mg/kg
APAP + Compound A, 10 mg/kg
APAP + NAC, 600 mg/kg

FIG. 3

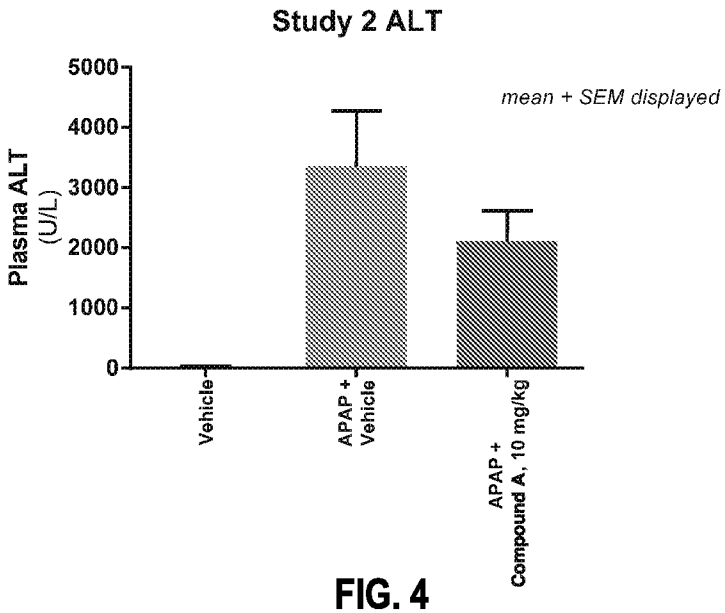
Study 2 ALT
mean + SEM displayed
Plasma ALT (U/L)
5000
4000
3000
2000
1000
0
Vehicle
APAP + Vehicle
APAP + Compound A, 10 mg/kg

FIG. 4

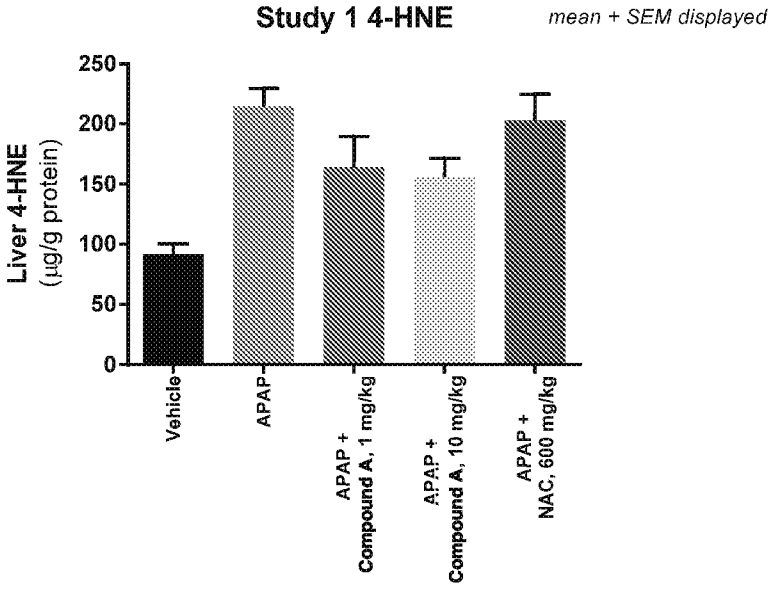
Study 1 4-HNE
mean + SEM displayed
Liver 4-HNE
(µg/g protein)
250
200
150
100
50
0
Vehicle
APAP
APAP + Compound A, 1 mg/kg
APAP + Compound A, 10 mg/kg
APAP + NAC, 600 mg/kg

FIG. 5

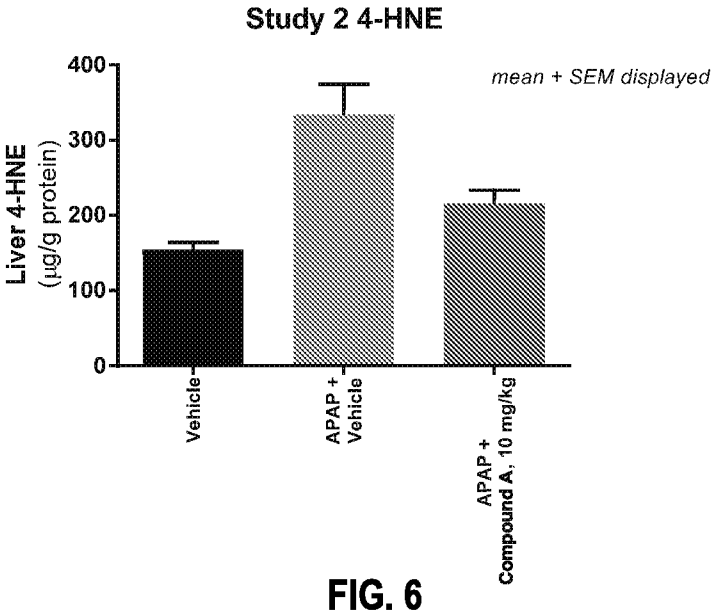
Study 2 4-HNE
mean + SEM displayed
Liver 4-HNE
(µg/g protein)
400
300
200
100
0
Vehicle
APAP + Vehicle
APAP + Compound A, 10 mg/kg

FIG. 6

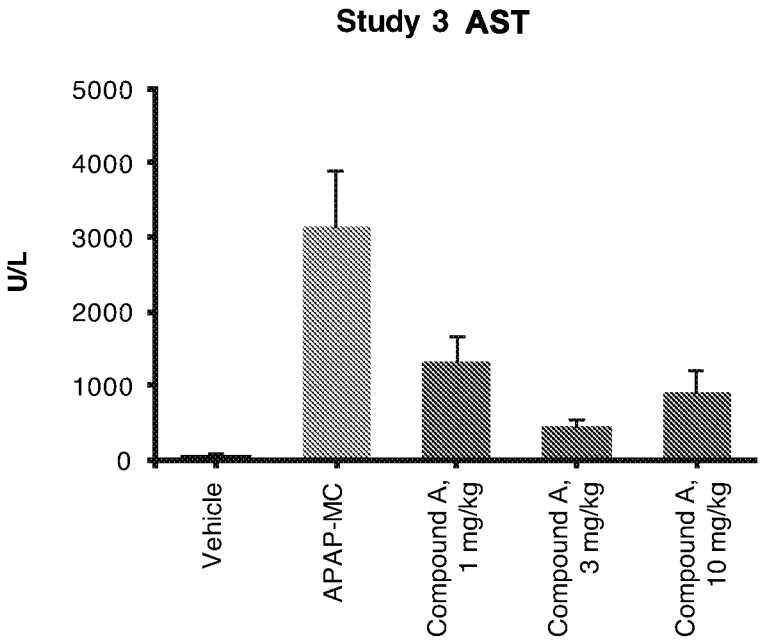
Study 3 AST
U/L
5000
4000
3000
2000
1000
0
Vehicle
APAP-MC
Compound A, 1 mg/kg
Compound A, 3 mg/kg
Compound A, 10 mg/kg

FIG. 7

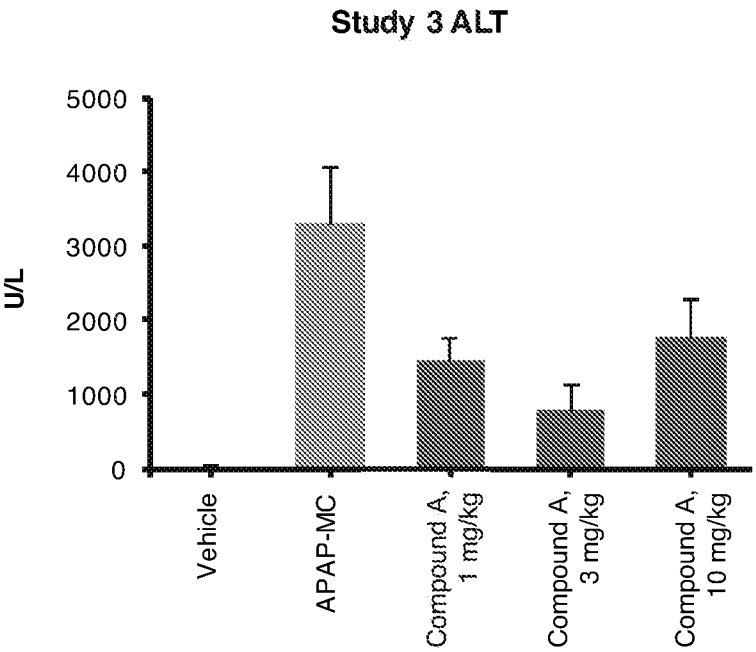
Study 3 ALT
U/L
5000
4000
3000
2000
1000
0
Vehicle
APAP-MC
Compound A, 1 mg/kg
Compound A, 3 mg/kg
Compound A, 10 mg/kg

FIG. 8

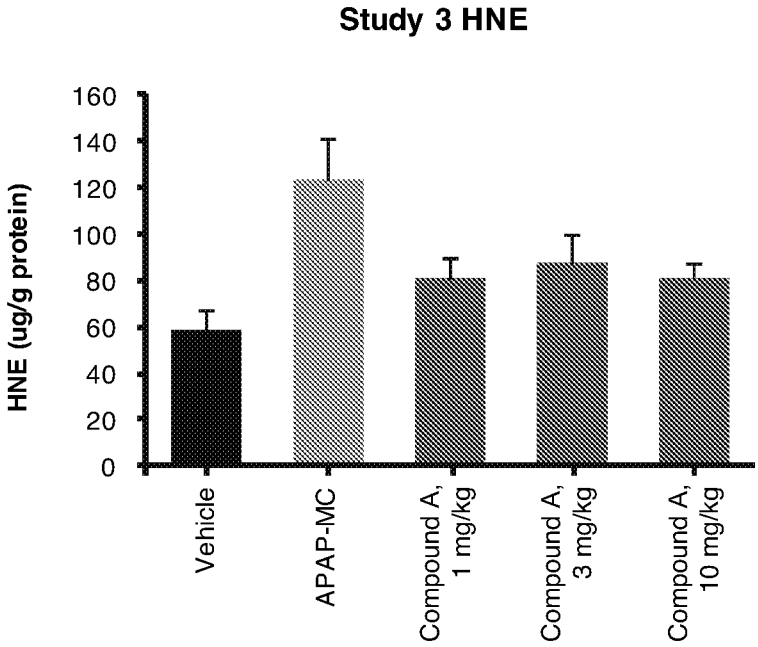
Study 3 HNE
HNE (ug/g protein)
160
140
120
100
80
60
40
20
0
Vehicle
APAP-MC
Compound A, 1 mg/kg
Compound A, 3 mg/kg
Compound A, 10 mg/kg

FIG. 9

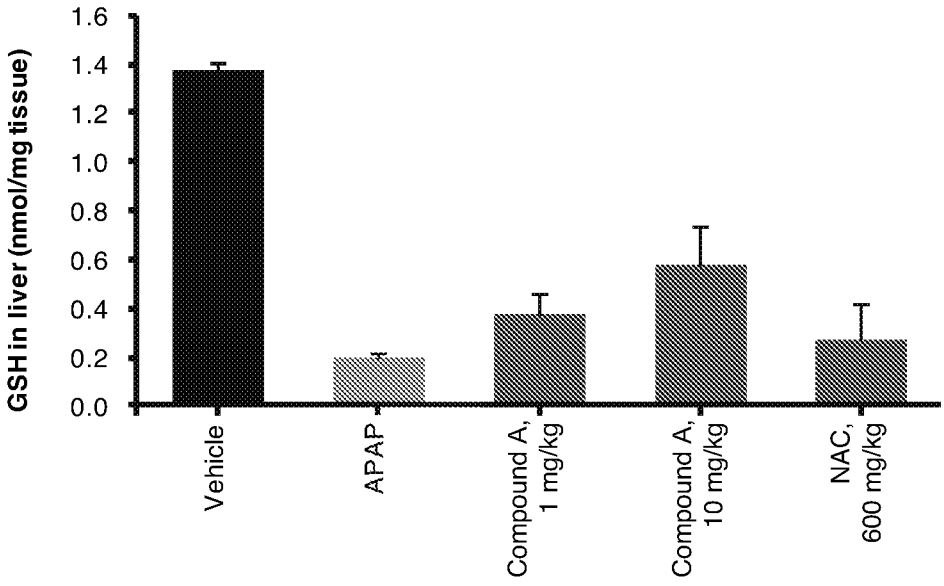
GSH in liver (nmol/mg tissue)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
APAP
Compound A, 1 mg/kg
Compound A, 10 mg/kg
NAC, 600 mg/kg

FIG. 10

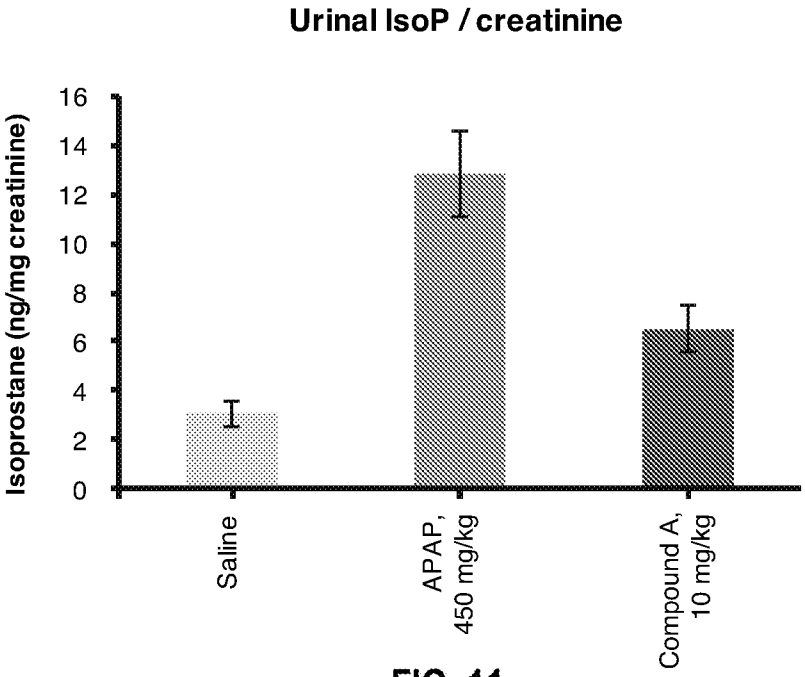
Urinal IsoP / creatinine
Isoprostane (ng/mg creatinine)
16
14
12
10
8
6
4
2
0
Saline
APAP, 450 mg/kg
Compound A, 10 mg/kg

FIG. 11

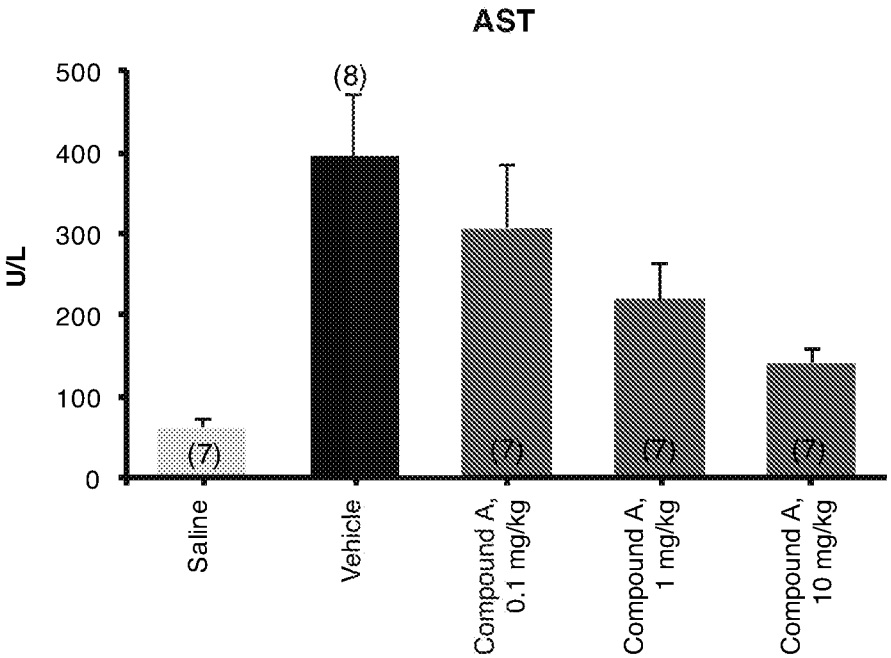
AST
U/L
500
400
300
200
100
0
(8)
(7)
(7)
(7)
(7)
Saline
Vehicle
Compound A, 0.1 mg/kg
Compound A, 1 mg/kg
Compound A, 10 mg/kg

FIG. 12

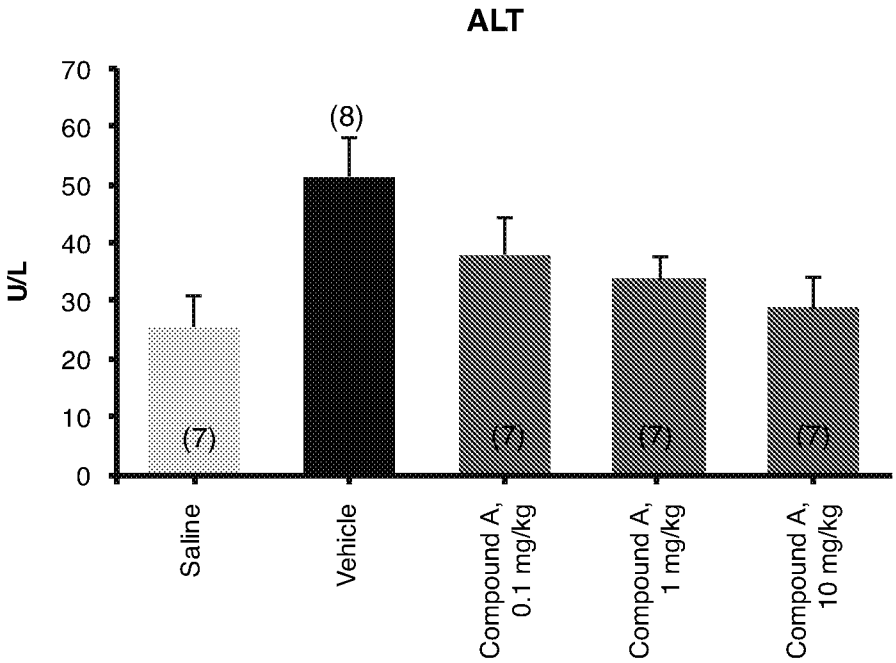
ALT
U/L
70
60
50
40
30
20
10
0
(8)
(7)
(7)
(7)
(7)
Saline
Vehicle
Compound A, 0.1 mg/kg
Compound A, 1 mg/kg
Compound A, 10 mg/kg

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/012706

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D413/04 C07D413/10 C07D471/08 C07D487/10
C07D265/38 A61P39/06 A61K31/536 C07D498/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/145118 A1 (EDISON PHARMACEUTICALS INC [US]) 18 September 2014 (2014-09-18) claims 1,23	1-74
A	WO 2016/133995 A1 (UNIV ARIZONA STATE [US]) 25 August 2016 (2016-08-25) claims 1,104	1-74
A	WO 2009/042270 A2 (UNIV BOSTON [US]; COTTAREL GUILLAUME [US]) 2 April 2009 (2009-04-02) cited in the application claim 20	1-74

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2018	20/03/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/012706

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014145118 A1	18-09-2014	CA 2906150 A1	18-09-2014
		EP 2970238 A1	20-01-2016
		HK 1220449 A1	05-05-2017
		JP 2016515527 A	30-05-2016
		US 2014275054 A1	18-09-2014
		WO 2014145118 A1	18-09-2014
WO 2016133995 A1	25-08-2016	AU 2016220096 A1	31-08-2017
		CA 2976776 A1	25-08-2016
		EP 3258938 A1	27-12-2017
		JP 2018505228 A	22-02-2018
		US 2018065941 A1	08-03-2018
		WO 2016133995 A1	25-08-2016
WO 2009042270 A2	02-04-2009	US 2011015137 A1	20-01-2011
		WO 2009042270 A2	02-04-2009