Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2736250 A1 2010/03/18

(21) 2 736 250

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2009/09/08
(87) Date publication PCT/PCT Publication Date: 2010/03/18
(85) Entrée phase nationale/National Entry: 2011/03/04
(86) N° demande PCT/PCT Application No.: US 2009/056254
(87) N° publication PCT/PCT Publication No.: 2010/030607
(30) Priorité/Priority: 2008/09/10 (US61/191,696)

(51) Cl.Int./Int.Cl. *A61K 31/05* (2006.01), *A61K 31/122* (2006.01), *A61P 25/00* (2006.01)

(71) Demandeur/Applicant:
EDISON PHARMACEUTICALS, INC., US

(72) Inventeurs/Inventors:
MILLER, GUY M., US;
KHEIFETS, VIKTORIA, US

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : TRAITEMENT DE TROUBLES GLOBAUX DU DEVELOPPEMENT GRACE A DES AGENTS THERAPEUTIQUES A ACTIVITE OXYDO-REDUCTRICE

(54) Title: TREATMENT OF PERVASIVE DEVELOPMENTAL DISORDERS WITH REDOX-ACTIVE THERAPEUTICS

(57) Abrégé/Abstract:
Methods of treating or suppressing pervasive developmental disorders (PDDs) including; autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) comprising administering to a subject in need thereof a therapeutically effective amount of one or more compounds as disclosed herein.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2010 (18.03.2010)

PCT

(10) International Publication Number
WO 2010/030607 A1

(51) International Patent Classification:
A61K 31/05 (2006.01) *A61P 25/00* (2006.01)
A61K 31/122 (2006.01)

(21) International Application Number:
PCT/US2009/056254

(22) International Filing Date:
8 September 2009 (08.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/191,696 10 September 2008 (10.09.2008) US

(71) Applicant *(for all designated States except US)*: **EDISON PHARMACEUTICALS, INC.** [US/US]; 5941 Optical Court, Suite 228, San Jose, CA 95138 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MILLER, Guy, M.** [US/US]; c/o Edison Pharmaceuticals, Inc., 5941 Optical Court, Suite 228, San Jose, CA 95138 (US). **KHEIFETS, Viktoria** [US/US]; c/o Edison Pharmaceuticals, Inc., 5941 Optical Court, Suite 228, San Jose, CA 95138 (US).

(74) Agents: **CERPA, Robert, K.** et al.; Morrison & Foerster LLP, 755 Pagen Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2010/030607 A1

(54) Title: TREATMENT OF PERVASIVE DEVELOPMENTAL DISORDERS WITH REDOX-ACTIVE THERAPEUTICS

(57) Abstract: Methods of treating or suppressing pervasive developmental disorders (PDDs) including; autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) comprising administering to a subject in need thereof a therapeutically effective amount of one or more compounds as disclosed herein.

TREATMENT OF PERVASIVE DEVELOPMENTAL DISORDERS WITH REDOX-ACTIVE THERAPEUTICS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 61/191,696 filed September 10, 2008. The content of that application is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The application discloses redox-active compositions and methods useful for treatment, prevention, or suppression of diseases, developmental delays and symptoms of pervasive developmental disorders including autistic spectrum disorders and/or attention deficit/hyperactivity disorder.

BACKGROUND OF THE INVENTION

[0003] Pervasive developmental disorder (PDD) is a category of neurological disorders characterized by severe and pervasive impairment in several areas of development, including social interaction and communications skills. The five disorders under PDD are autistic disorder (autism), Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS). Specific diagnostic criteria for each of these disorders can be found in the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV-TR) as distributed by the American Psychiatric Association (APA). Autistic spectrum disorder (ASD) is an umbrella term that is used to represent a broad heterogeneous disorder by collectively grouping autistic disorder, Asperger's syndrome and PDD-NOS.

[0004] Autism, the most common of the pervasive developmental disorders, affects an estimated 1 in approximately 150 births. Estimates of the prevalence of ASD are in the range of 6.5 to 6.6 per 1000 based on Autism and Developmental Disabilities Monitoring Network Surveillance (Year 2002). Indeed, as of 2003-2004, as many as 1.5 million Americans are believed to have some form of autism. Autism is a childhood encephalopathy characterized by deficiencies in social interaction and communication and by repetitive and stereotyped behaviors. Based on statistics from the U.S. Department of Education and other governmental agencies, autism is growing at a rate of 10-17 percent per year. At these rates,

the Autism Society of America (ASA) estimates that the prevalence of autism could easily reach 4 million Americans in the next decade.

[0005] Of the other four PDD forms, Asperger's syndrome is closest to autism in signs and likely causes; Rett's disorder and childhood disintegrative disorder share several signs with autism, but may have unrelated causes; PDD-not otherwise specified (PDD-NOS) is diagnosed when the criteria are not met for a more specific disorder (Lord C, *et al.* "Autism spectrum disorders" *Neuron* (2000) **28** (2): 355–63).

[0006] Autism is a complex serious developmental disability that interferes with, among other things, the normal development of the brain in the areas of social interaction and communication skills, and which causes severely restricted interests and repetitive behavior. Typically, autistic children and adults have difficulties in verbal and non-verbal communication, social interactions, and leisure or play activities. Autism can include language disorders with impaired understanding, echolalia, pronominal reversal (such as using "you" instead of "I" or "me" when referring to one's self), rituals and compulsive phenomena, and uneven intellectual development with mental retardation. Autistic children are also at increased risk of developing seizure disorders, especially during their teen years. Autism typically appears during the first three years of life and is the result of a neurological disorder that affects the functioning of the brain.

[0007] The overall incidence of autism is, for the most part, globally consistent. Indeed, autism knows no racial, ethnic, or social boundaries, and family income, lifestyle, and educational levels do not affect the chance of autism's occurrence. However, it has been found to be four times more prevalent in boys than girls. On the other hand, Rett's disorder is more prevalent in girls than boys.

[0008] Since being first described by Dr. Leo Kanner in 1943, the understanding of autism has grown tremendously. Although autism is defined by a certain set of behaviors, it is a spectrum disorder in that its symptoms and characteristics can be present in a wide variety of combinations, from mild to severe. Therefore, autistic children and adults can exhibit any combination of the behaviors in any degree of severity. Two individuals, both with the same diagnosis, may have varying skills and display very different actions. Those only mildly affected may exhibit slight delays in language or communication and may face greater challenges in social interactions. For example, one may have difficulty initiating and/or

maintaining a conversation. Communication by autistic children or adults is often displayed as talking at others (for example, a monologue on a favorite subject that continues despite attempts by others to interject comments).

[0009] Autism seems to cause those affected by it to process and respond to information in unique ways. In some individuals with PDD including autism, aggressive and/or self-injurious behavior may exist. The following traits, as identified by the ASA, may also be present in persons with autism: insistence on sameness or resistance to change; difficulty in expressing needs (i.e. uses gestures or pointing instead of words); repeating words or phrases in place of normal, responsive language; laughing, crying, or showing distress for reasons not apparent to others; preferring to be alone or an aloof manner; tantrums; difficulty in mixing with others; not wanting to cuddle or be cuddled; little or no eye contact; unresponsive to normal teaching methods; sustained odd play; spinning objects; inappropriate attachments to objects; apparent over-sensitivity or under-sensitivity to pain; no real fears of danger; marked physical over-activity or extreme under-activity; uneven gross/fine motor skills; and/or non-responsiveness to verbal cues (i.e. acts as if deaf although hearing tests in normal range).

[0010] Symptoms as in attention deficit hyperactivity disorder (ADHD) are frequent among individuals with pervasive developmental disorders (PDD). Children meeting diagnostic criteria for a pervasive developmental disorder (PDD) display symptoms and impairment related to attention deficit hyperactivity disorder (ADHD) sufficient to warrant a diagnosis of ADHD (Goldstein S, *et al* " The Comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: Results of a Retrospective Chart Review" *Journal of Autism and Developmental Disorders,* (2004) **34** (3) :329-339). Hattori J, *et al* " Are Pervasive Developmental Disorders and Attention Deficit/Hyperactivity Disorder Distinct Disorders?" studied the relationship between patients with attention deficit/hyperactivity disorder (ADHD) and those with pervasive developmental disorders (PDD), using the High-Functioning Autism Spectrum Screening Questionnaire (ASSQ) and ADHD Rating Scale-IV. The patients with strictly diagnosed ADHD had many PDD-related symptoms, and the patients with PDD had many ADHD-related symptoms. It therefore seems difficult to make a distinction between ADHD and PDD by using the present diagnostic criteria in the DSM-IV.

[0011] People with autism have social impairments that appear early in childhood and continue through adulthood. Autistic infants show less attention to social stimuli, smile and

look at others less often, and respond less to their own name. Autistic toddlers have more striking social deviance; for example, they have less eye contact and anticipatory postures and are more likely to communicate by manipulating another person's hand (Volkmar F, *et al* "Autism in infancy and early childhood," *Annu Rev Psychol* (2005) **56**: 315–36.) Three- to five-year-old autistic children are less likely to exhibit social understanding, approach others spontaneously, imitate and respond to emotions, communicate nonverbally, and take turns with others. However, they do form attachments to their primary caregivers. (Sigman M, *et al*. "Early detection of core deficits in autism" *Ment Retard Dev Disabil Res Rev*. (2004) **10** (4): 221–33). They display moderately less attachment security than usual, although this feature disappears in children with higher mental development or less severe autism spectrum disorders. Older children and adults with ASD perform worse on tests of face and emotion recognition (Sigman M. *et al*, see supra). Contrary to common belief, autistic children do not prefer to be alone. Making and maintaining friendships often proves to be difficult for those with autism. For them, the quality of friendships, not the number of friends, predicts how lonely they are.

[0012] Unlike those with autism, people with Asperger's syndrome are not usually withdrawn around others; they approach others, even if awkwardly, for example by engaging in a one-sided, long-winded speech about a favorite topic while being oblivious to the listener's feelings or reactions, such as signs of boredom or haste to leave.

[0013] About a third to a half of individuals with autism does not develop enough natural speech to meet their daily communication needs; (Noens I, *et al*, "The ComFor: an instrument for the indication of augmentative communication in people with autism and intellectual disability". *J Intellect Disabil Res* (2006) 50 (9): 621–32.) Differences in communication may be present from the first year of life, and may include delayed onset of babbling, unusual gestures, diminished responsiveness, and the desynchronization of vocal patterns with the caregiver. In the second and third years, autistic children have less frequent and less diverse babbling, consonants, words, and word combinations; their gestures are less often integrated with words. Autistic children are less likely to make requests or share experiences, and are more likely to simply repeat others' words or reverse pronouns.

[0014] For individuals with autism, sensory integration problems are common. In particular, their senses may be either over- or under-active. The fuzz of a kiwi may actually be experienced as painful; a sweet, fruity smell may cause a gagging reflex. Some children or

adults with autism are particularly sensitive to sound, so that even the most ordinary daily noises are painful.

[0015] Although there is no single known cause for autism, it is generally accepted that it is caused by abnormalities in brain structure or function. The shape and structure of the brain in autistic versus non-autistic children show differences when brain scans are viewed. Currently the links between heredity, genetics and medical problems are being investigated by researchers, as well as a number of other theories. The theory of a genetic basis of the disorder is supported by the fact that, in many families, there appears to be a pattern of autism or related disabilities. While no one gene has been identified as causing autism, researchers are searching for irregular segments of genetic code that autistic children may have inherited. While researchers have not yet identified a single trigger that causes autism to develop, it also appears that some children are born with a susceptibility to autism.

[0016] Other researchers are investigating the possibility that under certain conditions, a cluster of unstable genes may interfere with brain development resulting in autism. Still other researchers are investigating problems during pregnancy or delivery as well as environmental factors such as viral infections, metabolic imbalances, and exposure to environmental chemicals. Yet other researchers are investigating the link between autism and chemical toxicity, in particular with the mercury-containing vaccine preservative thimerosal.

[0017] Some cases of autism have been associated with several different organic conditions, including bioenergetic metabolism deficiency suggested by the detection of high lactate levels in some patients (Coleman M. et al, Autism and Lactic Acidosis, *J. Autism Dev Disord.*, (1985) **15**: 1-8; Laszlo *et al* Serum serotonin, lactate and pyruvate levels in infantile autistic children, *Clin. Chim. Acta* (1994) **229**:205-207; and Chugani *et al.*, Evidence of altered energy metabolism in autistic children, *Progr. Neuropsychopharmacol Biol Psychiat.*, (1999) **23**:635-641) and by nuclear magnetic resonance imagining as well as positron emission tomography scanning which documented abnormalities in brain metabolism. Although the mechanism of hyperlactacidemia remains unknown, a likely possibility involves mitochondrial oxidative phosphorylation dysfunction in neuronal cells. A small subset of autistic patients diagnosed with deficiencies in complex I or III of the respiratory chain have been reported in the literature (see Oliveira, G., *Developmental Medicine & Child Neurology* (2005) **47** 185-189; and Filipek, PA *et al.*, *Journal of Autism and Developmental Disorders* (2004) **34**:615-623.) However, in many of the cases of autism where there is some

evidence of mitochondrial dysfunction, there is an absence of the classic features associated with mitochondrial disease, such as mitochondrial pathology in muscle biopsy (see Rossignol, D.A. *et al.*, *Am J. Biochem. & Biotech*, **4** (2) 208-217).

[0018] The main goals of treatment are to lessen associated deficits and family distress, and to increase quality of life and functional independence. No single treatment is best and treatment is typically tailored to the child's needs. Intensive, sustained special education programs and behavior therapy early in life can help children acquire self-care, social, and job skills, (Myers SM, *et al.* "Management of children with autism spectrum disorders" *Pediatrics* (2007) **120** (5): 1162–82) and Angley M, *et al.* "Children and autism—part 1—recognition and pharmacological management" *Aus.t Fam. Physician* (2007) **36** (9): 741–4) and often improve functioning and decrease symptom severity and maladaptive behaviors ; (Rogers SJ, *et al.*,. "Evidence-based comprehensive treatments for early autism" *J Clin. Child Adolesc. Psychol.* (2008) **37** (1): 8–38).

[0019] Medications have not been proven to correct deficits of ASDs and are not the primary treatment. They are used to treat problems associated with autism disorders, such as associated maladaptive behaviors or psychiatric comorbidities that may interfere with educational progress, socialization, health or safety and quality of life. More than half of U.S. children diagnosed with autistic disorders are prescribed psychoactive drugs or anticonvulsants, with the most common drug classes being antidepressants, stimulants, and antipsychotics.(Oswald DP, *et al.* "Medication Use Among Children with Autism Spectrum Disorders". *J Child Adolesc Psychopharmacol* (2007) **17** (3): 348–55.) Aside from antipsychotics, there is scant reliable research about the effectiveness or safety of drug treatments for children, adolescents or adults with ASD. A person with ASD may respond atypically to medications, the medications can have adverse effects, and no known medication relieves autism's core symptoms of social and communication impairments. Alternative nutritional therapies for autistic children may include Idebenone and CoQ10, because of their superior antioxidant properties, but no studies have been performed to prove their efficacy.

[0020] US Patent Publication 2005/0203066 discloses compounds, compositions and methods for treatment of developmental delay in cognitive, motor, language, executive function or social skills with a pyrimidine nucleotide precursor, but it does not disclose any compounds, compositions or methods of treatment with compounds of the present invention.

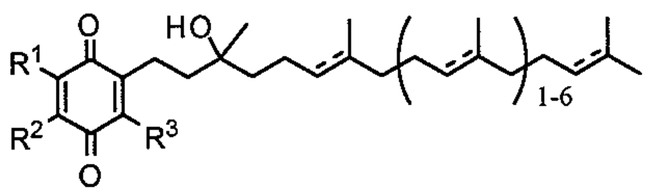
[0021] Attention deficit hyperactivity disorder (ADHD) - also referred to as ADD - is a biological, brain based condition that is characterized by poor attention and distractibility and/or hyperactive and impulsive behaviors. It is one of the most common mental disorders that develop in children. Symptoms may continue into adolescence and adulthood. If left untreated, ADHD can lead to poor school/work performance, poor social relationships and a general feeling of low self esteem. The most prevalent symptoms of ADHD are inattention and distractibility and/or hyperactive and impulsive behaviors. Difficulties with concentration, mental focus, and inhibition of impulses and behaviors are chronic and pervasive and impair an individual's daily functioning across various settings - home, school or work, in relationships, etc. ADD or attention deficit disorder is a general term frequently used to describe individuals that have attention deficit hyperactivity disorder (ADHD) without the hyperactive and impulsive behaviors. The terms are often used interchangeably for both those who do and those who do not have symptoms of hyperactivity and impulsiveness.

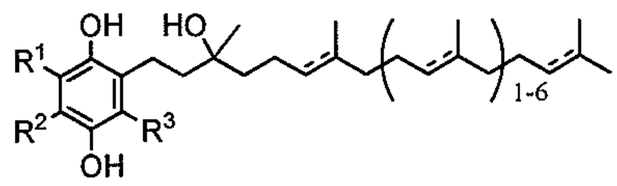
[0022] Thus, there is an unmet need for improved methods of treating patients with pervasive developmental disorders, particularly with autism and/or attention deficit/hyperactivity disorder (ADHD).

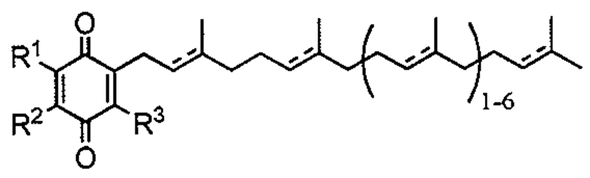
SUMMARY OF THE INVENTION

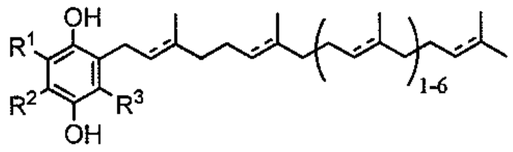
[0023] The present invention provides methods and redox-active compositions that can reduce the symptoms of autism in a human patient. Briefly, the methods and compositions comprise administering a physiologically effective amount of one or both of in sufficient quantities to reduce the effects of the autism. When administered to human patients suffering from autism, without restriction on the normal diet of the patients, the compositions and methods reduce or improve one or more symptoms of autism, such as increased eye contact, better enunciation and use of pronouns, less fatigue, singing a song for the first time with the melody and words together and the entire song understandable, playing with age appropriate friends for the first time, fewer tantrums, better sleep patterns, improved politeness and coordination, being more loving, acknowledging another individual's emotion, and increased voice and word association. The redox-active compounds of the present invention are superior because they show protective effect not only on cells of autistic patients that have a mitochondrial dysfunction but also on cells of patients that do not show any impairment of mitochondrial energy metabolism.

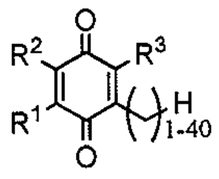
[0024] In one aspect, the invention embraces a composition for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-Not Otherwise Specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment comprising one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI or mixtures thereof,

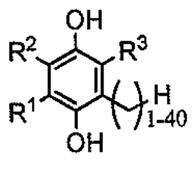

(I)


(II)


(III)


(IV)


(V)


(VI)

wherein,

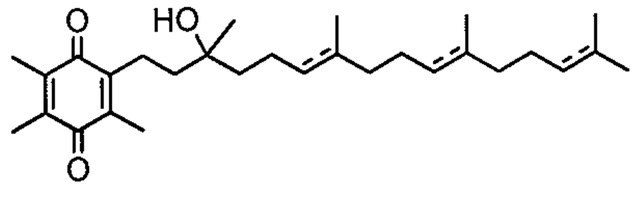
the bonds indicated with a dashed line can independently be single or double;

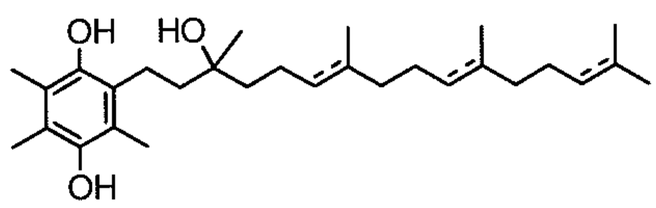
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

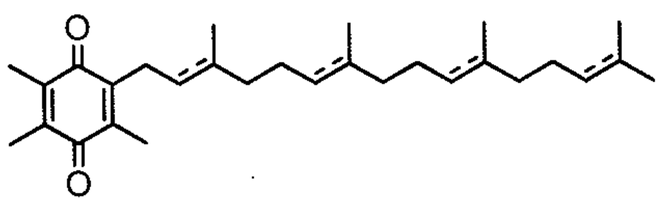
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

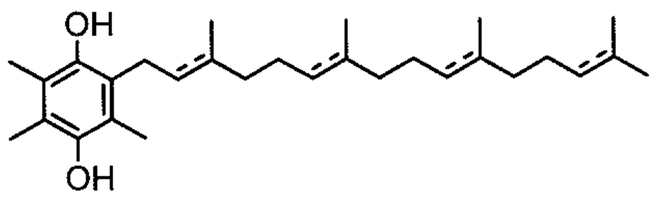
[0025] In one embodiment, R^1, R^2, and R^3 are independently selected from $(C_1\text{-}C_4)$alkyl, and in a particular example R^1, R^2, and R^3 are methyl. In another embodiment, at least one of R^1, R^2, and R^3 is not methyl. In another embodiment, R^1 and R^2 are independently selected from $(C_1\text{-}C_4)$alkoxy, and R^3 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^1 and R^2 are methoxy, and R^3 is methyl.

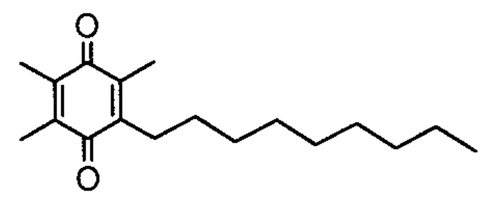
[0026] In one embodiment, the invention embraces a composition for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment comprising one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,

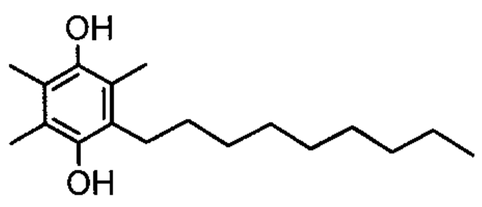

(Ia)


(IIa)


(IIIa)


(IVa)

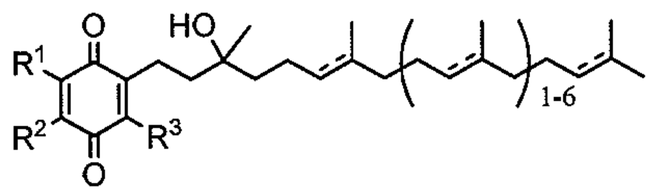

(Va)

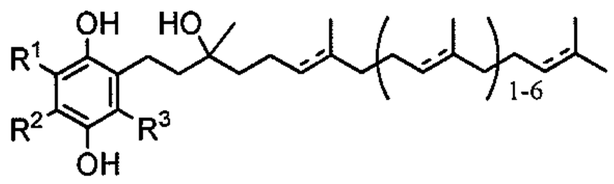

(VIa)

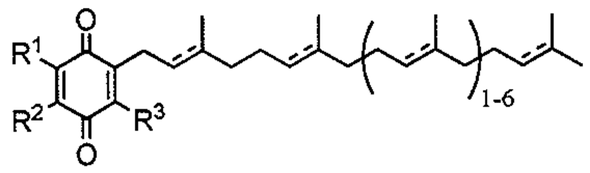
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all

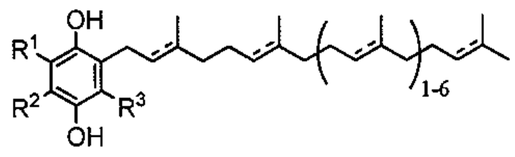
single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

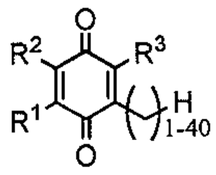
[0027] In another aspect, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, or mixtures thereof,

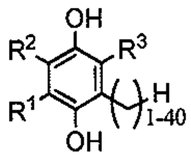

(I)


(II)


(III)


(IV)


(V)


(VI)

wherein,

the bonds indicated with a dashed line can independently be single or double;

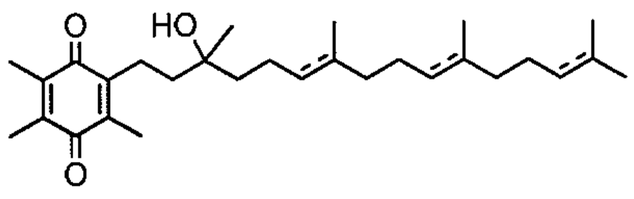
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all

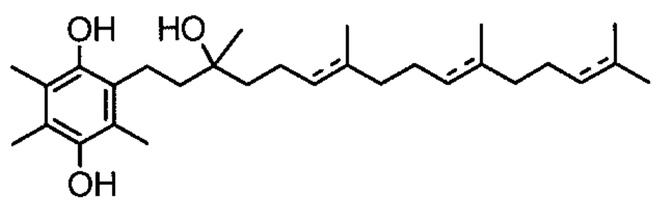
single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

[0028] In one embodiment, R^1, R^2, and R^3 are independently selected from $(C_1\text{-}C_4)$alkyl, and in a particular example R^1, R^2, and R^3 are methyl. In another embodiment, at least one of R^1, R^2, and R^3 is not methyl. In another embodiment, R^1 and R^2 are independently selected from $(C_1\text{-}C_4)$alkoxy, and R^3 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^1 and R^2 are methoxy, and R^3 is methyl.

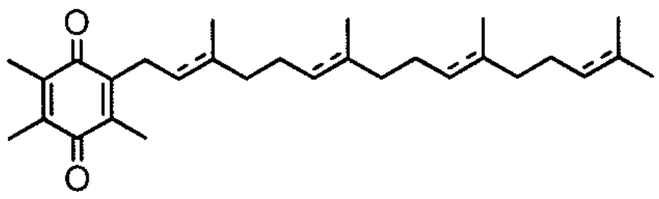
[0029] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,



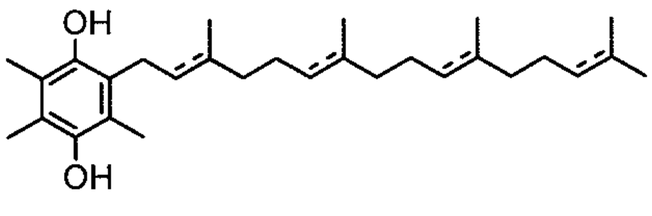
(Ia)



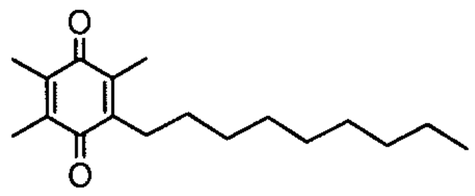
(IIa)



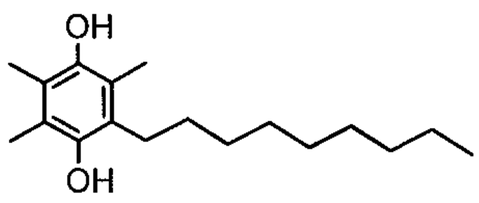
(IIIa)



(IVa)



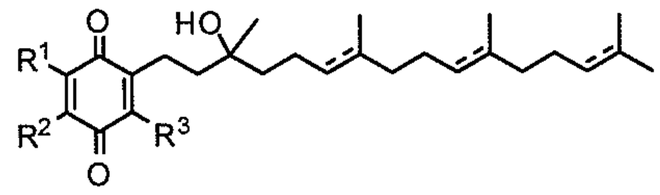
(Va)



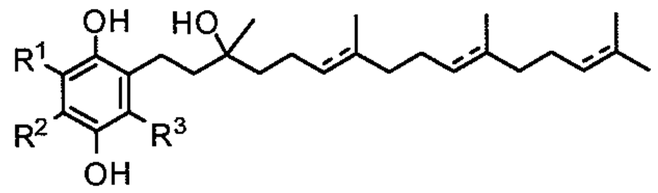
(VIa)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

[0030] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds of Formula Id, Formula IId or mixtures thereof,



(Id)



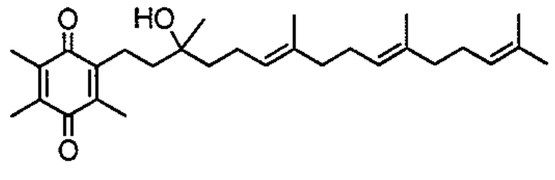
(IId)

wherein,
the bonds indicated with a dashed line can independently be single or double;
R^1, R^2, and R^3 are independently selected from H, $(C_1\text{-}C_4)$alkyl, and $(C_1\text{-}C_4)$alkoxy;
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

[0031] In one embodiment, R^1, R^2, and R^3 are independently selected from $(C_1\text{-}C_4)$alkyl, and in a particular example R^1, R^2, and R^3 are methyl. In another embodiment, at least one of R^1, R^2, and R^3 is not methyl. In another embodiment, R^1 and R^2 are independently selected from $(C_1\text{-}C_4)$alkoxy, and R^3 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^1 and R^2 are methoxy, and R^3 is methyl.

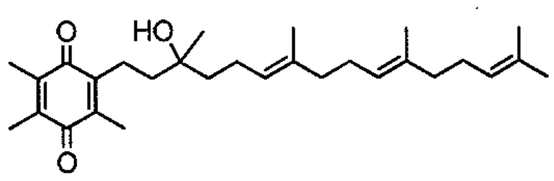
[0032] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder

(CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ib:


(Ib)

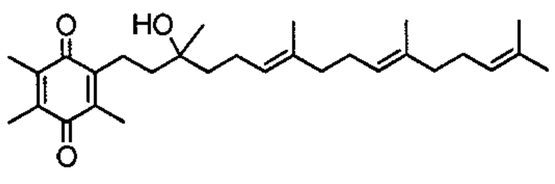
which is named 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione;
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In particular, the stereoisomers 2-((3R,6E,10E)-3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10-dienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione and 2-((3S,6E,10E)-3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10-dienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (abbreviated as Ib-R and Ib-S, respectively) are included in this embodiment.

[0033] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ib:


(Ib)

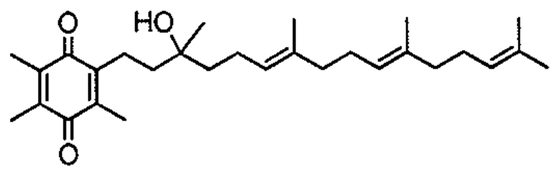
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ib-R and Ib-S.

[0034] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ib:


(Ib)

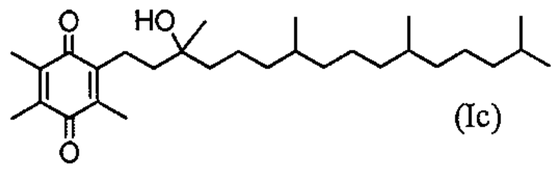
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ib-R and Ib-S.

[0035] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ib:


(Ib)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ib-R and Ib-S.

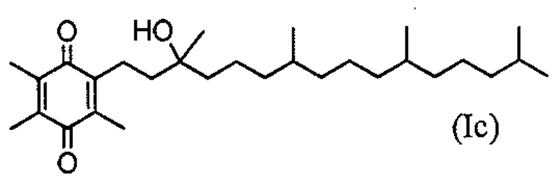
[0036] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ic:


(Ic)

which is named 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In particular, the stereoisomers 2-((3R,7R,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3S,7R,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3R,7S,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3R,7R,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3S,7S,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3S,7R,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; 2-((3R,7S,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-

trimethylcyclohexa-2,5-diene-1,4-dione; and 2-((3S,7S,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione; (referred to as Ic-RRR, Ic-SRR, Ic-RSR, Ic-RRS, Ic-SSR, Ic-SRS, Ic-RSS, and Ic-SSS, respectively) are included in this embodiment.

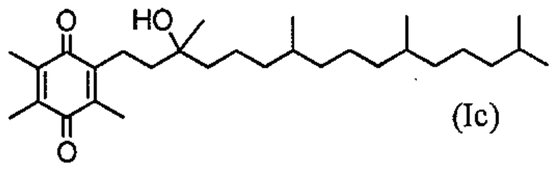
[0037] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing an autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ic:



(Ic)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ic-RRR, Ic-SRR, Ic-RSR, Ic-RRS, Ic-SSR, Ic-SRS, Ic-RSS, and Ic-SSS.

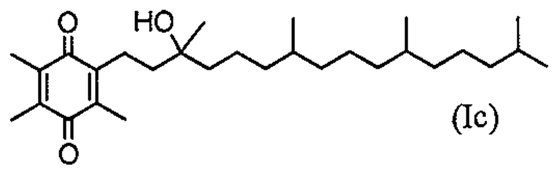
[0038] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ic:



(Ic)

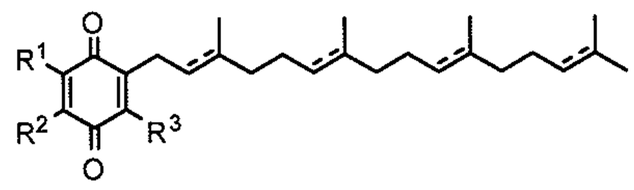
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ic-RRR, Ic-SRR, Ic-RSR, Ic-RRS, Ic-SSR, Ic-SRS, Ic-RSS, and Ic-SSS.

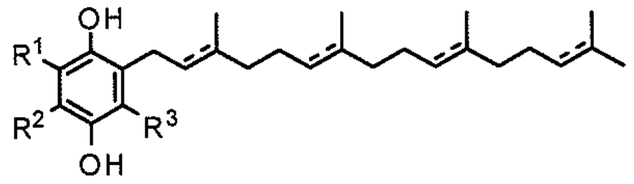
[0039] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Ic:


(Ic)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as Ic-RRR, Ic-SRR, Ic-RSR, Ic-RRS, Ic-SSR, Ic-SRS, Ic-RSS, and Ic-SSS.

[0040] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds of Formula IIId, Formula IVd or mixtures thereof,


(IIId)


(IVd)

wherein,

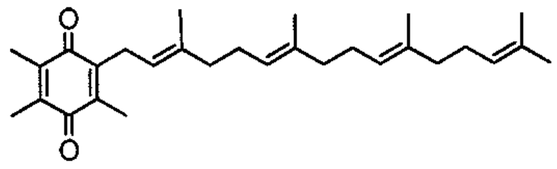
the bonds indicated with a dashed line can independently be single or double,

R^1, R^2, and R^3 are independently selected from H, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy;

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

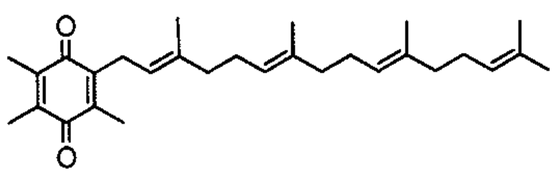
[0041] In one embodiment, R^1, R^2, and R^3 are independently selected from $(C_1\text{-}C_4)$alkyl, and in a particular example R^1, R^2, and R^3 are methyl. In another embodiment, at least one of R^1, R^2, and R^3 is not methyl. In another embodiment, R^1 and R^2 are independently selected from $(C_1\text{-}C_4)$alkoxy, and R^3 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^1 and R^2 are methoxy, and R^3 is methyl.

[0042] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIb:


(IIIb)

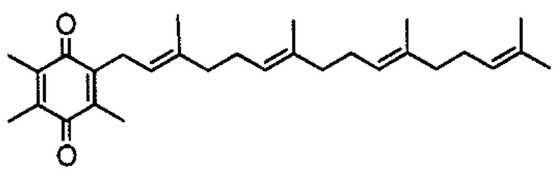
which is named 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione; and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

[0043] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing an autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIb:


(IIIb)

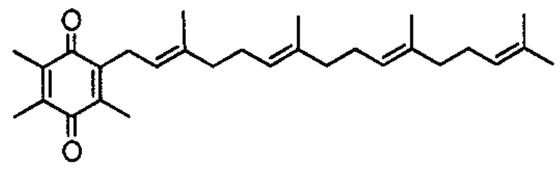
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

[0044] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIb:


(IIIb)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

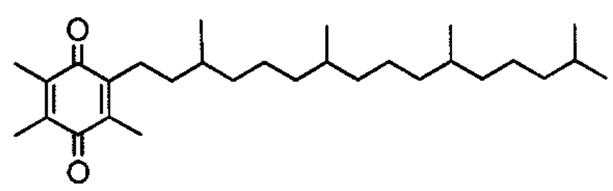
[0045] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIb:



(IIIb)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

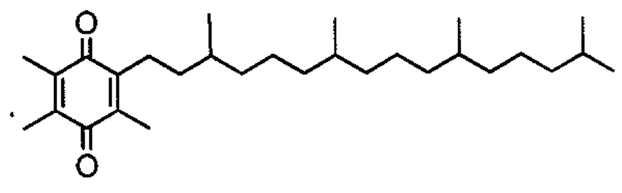
[0046] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIc:



(IIIc)

which is named 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof. In particular, the stereoisomers 2,3,5-trimethyl-6-((3R,7R,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3S,7R,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3R,7S,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3R,7R,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3S,7S,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3S,7R,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; 2,3,5-trimethyl-6-((3R,7S,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione; and 2,3,5-trimethyl-6-((3S,7S,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (abbreviated as IIIc-RRR, IIIc-SRR, IIIc-RSR, IIIc-RRS, IIIc-SSR, IIIc-SRS, IIIc-RSS, and IIIc-SSS, respectively) are included in this embodiment.

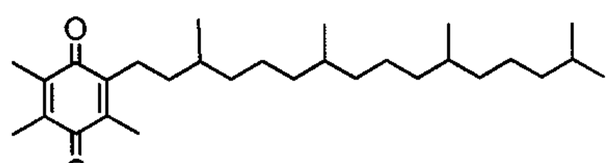
[0047] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing an autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIc:



(IIIc)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as IIIc-RRR, IIIc-SRR, IIIc-RSR, IIIc-RRS, IIIc-SSR, IIIc-SRS, IIIc-RSS, and IIIc-SSS.

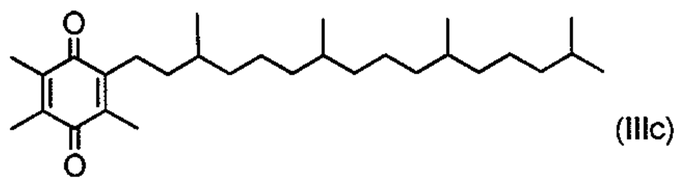
[0048] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIc:



(IIIc)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as IIIc-RRR, IIIc-SRR, IIIc-RSR, IIIc-RRS, IIIc-SSR, IIIc-SRS, IIIc-RSS, and IIIc-SSS.

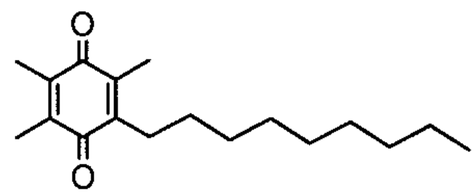
[0049] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula IIIc:



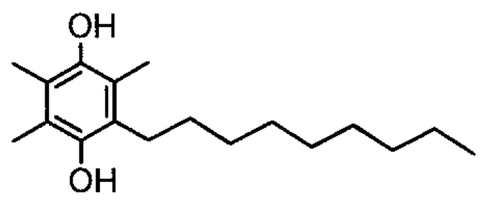
(IIIc)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof, such as IIIc-RRR, IIIc-SRR, IIIc-RSR, IIIc-RRS, IIIc-SSR, IIIc-SRS, IIIc-RSS, and IIIc-SSS.

[0050] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Va or Formula VIa or mixtures thereof:



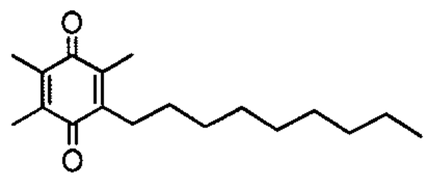
(Va)



(VIa)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

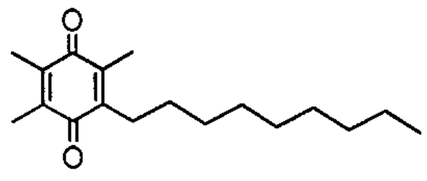
[0051] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Va:



(Va)

which is named 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione; and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

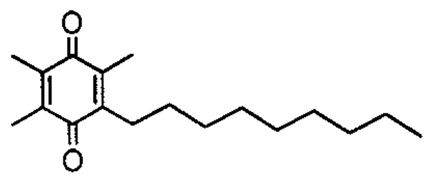
[0052] In another aspect, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing an autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Va:



(Va)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

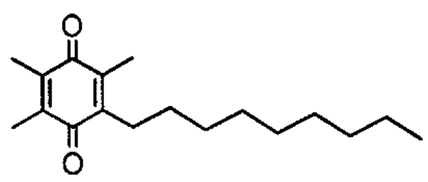
[0053] In another aspect, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Va:



(Va)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

[0054] In another aspect, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of a compound of Formula Va:



(Va)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof.

[0055] In another embodiment the invention embraces a composition wherein the compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR;

IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

[0056] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD), in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

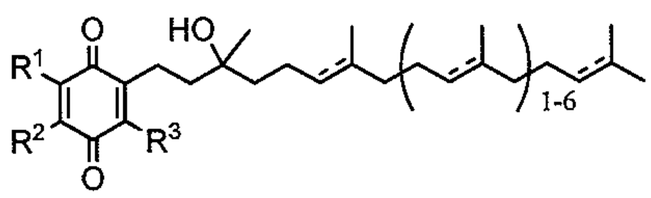
[0057] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing an autistic spectrum disorder (ASD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

[0058] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing autism in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-

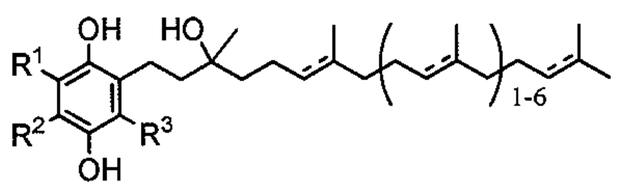
3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

[0059] In another embodiment, the invention embraces a method of reducing the symptoms associated with, or of treating or suppressing attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

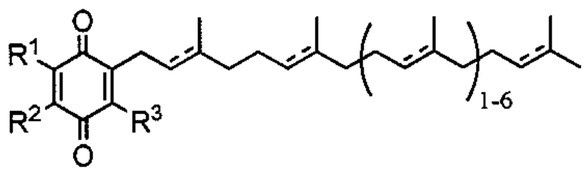
[0060] In another embodiment, the invention embraces the use of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, or mixtures thereof,



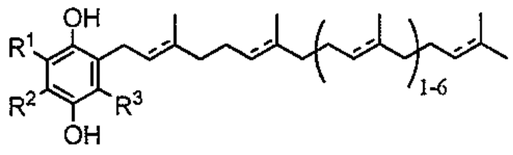
(I)



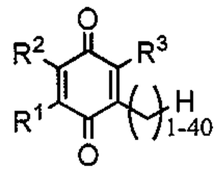
(II)

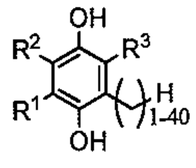


(III)



(IV)


(V)


(VI)

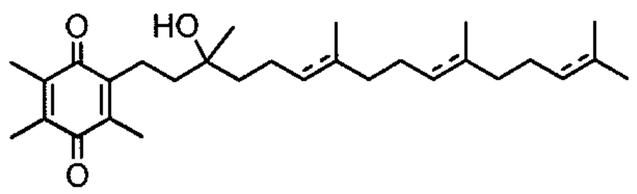
wherein,

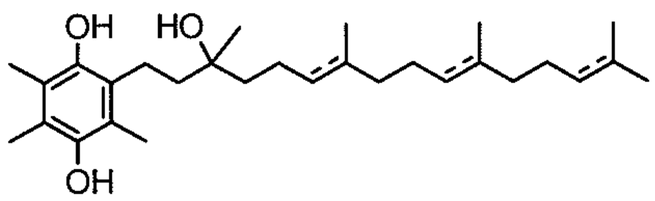
the bonds indicated with a dashed line can independently be single or double;

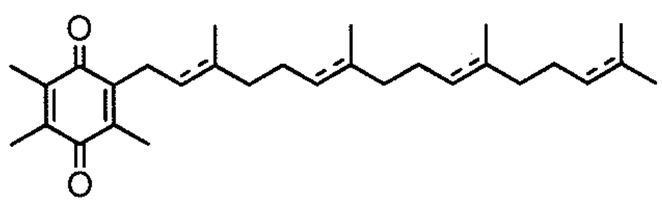
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

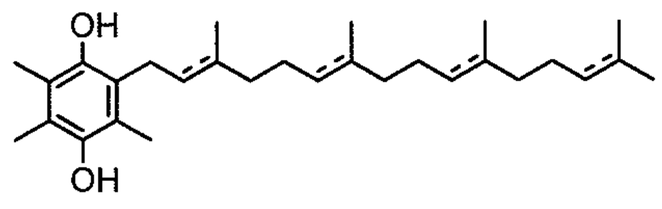
and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof; for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) in a patient in need of such treatment. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

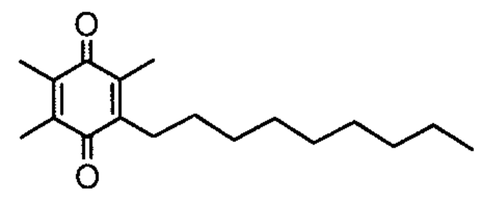
[0061] In another embodiment, the invention embraces the use of one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,


(Ia)

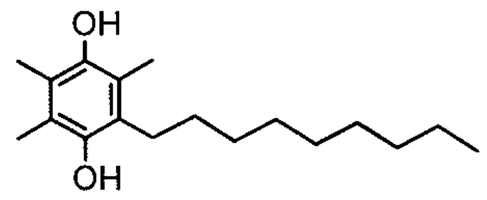

(IIa)


(IIIa)


(IVa)



(Va)



(VIa)

and all salts, stereoisomers, mixtures of stereoisomers, prodrugs, metabolites, solvates and hydrates thereof; for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) in a patient in need of such treatment. In another embodiment, the bonds indicated with a dashed line are all single bonds. In another embodiment, the bonds indicated with a dashed line are all double bonds.

[0062] In another embodiment, the invention embraces the use of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) in a patient in need of such treatment.

[0063] In any of the foregoing embodiments, the pervasive developmental disorder (PDD) can be selected from autistic spectrum disorder (ASD).

[0064] In any of the foregoing embodiments, the disorder can be attention deficit/hyperactivity disorder (ADHD)

[0065] In any of the foregoing embodiments, the symptoms treated by the compounds of the present invention are selected from the group of symptoms consisting of eye contact avoidance, failure to socialize, attention deficit, poor mood, hyperactivity, anxiety, stimming, poor comprehension, inappropriate speech, abnormal sound sensitivity, poor digestion,

disrupted sleep, and perseveration, and where the decreased incidence is measured relative to the incidence in the untreated individual.

[0066] In one embodiment, the present invention provides pharmaceutical compositions able to reduce the symptoms of autism in a patient, comprising a physiologically effective amount of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd, and at least one of the group consisting of a physiologically acceptable carrier, adjuvant, excipient, buffer and diluent.

[0067] In still a further aspect, the present invention provides foods, medical foods, functional foods, food supplements, or dietary supplements comprising compositions of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd, and at least one of the group consisting of a physiologically or nutritionally acceptable carrier, adjuvant, excipient, buffer and diluent. In one embodiment, the invention comprises a method of administering a therapeutically effective amount or physiologically effective amount of the foods, medical foods, functional foods, food supplements, or dietary supplements to a patient in need thereof. In another embodiment, the invention comprises a method of reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorder (PDD), including autistic disorder, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett's disorder, and PDD-Not Otherwise Specified (PDD-NOS); or attention deficit/hyperactivity disorder (ADHD), by administering a therapeutically effective amount or physiologically effective amount of the foods, medical foods, functional foods, food

supplements, or dietary supplements to a patient in need thereof, especially for reducing the symptoms associated with, or for treating or suppressing, autistic spectrum disorder (ASD); or for reducing the symptoms associated with or for treating or suppressing, attention deficit/hyperactivity disorder (ADHD).

[0068] In yet another aspect, the invention also provides articles of manufacture and kits containing materials useful for treating or suppressing autistic spectrum disorder. The invention also provides kits comprising any one or more of the compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd. In some embodiments, the kit of the invention comprises the container described above.

[0069] In other aspects, the kits may be used for any of the methods described herein, including, for example, to treat an individual with ASD disorder, or to suppress an ASD disorder in an individual.

[0070] In one embodiment, the invention also embraces modulating one or more autism biomarkers, normalizing one or more autism biomarkers, or enhancing one or more autism biomarkers, comprising administering to a subject a therapeutically effective amount or physiologically effective amount of one or more compounds or compositions as described herein. The invention also embraces compounds and compositions as described herein, which are useful for modulating one or more autism biomarkers, normalizing one or more autism biomarkers, or enhancing one or more autism biomarkers.

[0071] The present invention comprises multiple aspects, features and embodiments; where such multiple aspects, features and embodiments can be combined and permuted in any desired manner.

[0072] These and other aspects, features and embodiments of the present invention will become evident upon reference to the remainder of this application, including the following detailed description. In addition, various references are set forth herein that describe in more

detail certain compositions, and/or methods; all such references are incorporated herein by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

[0073] The present invention provides methods and compositions able to reduce the symptoms of pervasive developmental disorder including autistic spectrum disorder or attention deficit/hyperactivity disorder (ADHD) in a patient, including a human patient. Briefly, the compositions and methods comprise administering a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd to a human patient in sufficient quantities to reduce the effects of the autistic disease or of the attention deficit disorder. An initial trial wherein compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd are administered to human patients, without restriction on the normal diet of the patients, would provide a significant number of the patients with a significant reduction of one or more symptoms, such as increased eye contact, better enunciation and use of pronouns, less fatigue, singing a song for the first time with the melody and words together and the entire song understandable, playing with age appropriate friends for the first time, fewer tantrums, better sleep patterns, improved politeness and coordination, being more loving, acknowledging another individual's emotion, increased voice and word association.

[0074] By "subject," "individual," or "patient" is meant an individual, more preferably a mammal, most preferably a human.

[0075] "Treating" a disease 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 disease or one or more symptoms of the disease, or to retard the progression of the disease or of one or more symptoms of the disease, or to reduce the severity of the disease or of one or more symptoms of the disease. "Suppression" of a disease 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 disease, or to suppress the manifestation of adverse symptoms of the disease. The distinction between treatment and suppression is that treatment occurs after adverse symptoms of the disease are manifest in a subject, while suppression occurs before adverse symptoms of the disease are manifest in a subject. Suppression may be partial, substantially total, or total. Because the autism disorders are inherited, genetic screening can be used to identify patients at risk of the disease. The compounds and methods of the invention can then be administered to asymptomatic patients at risk of developing the clinical symptoms of the disease, in order to suppress the appearance of any adverse symptoms.

[0076] "Therapeutic use" of the compounds discussed herein is defined as using one or more of the compounds discussed herein to treat or suppress a disease, as defined above. 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 disease or one or more symptoms of a disease, or to retard the progression of a disease or of one or more symptoms of a disease, or to reduce the severity of a disease or of one or more symptoms of a disease, or to suppress the clinical manifestation of a disease, or to suppress the manifestation of adverse symptoms of a disease. A therapeutically effective amount can be given in one or more administrations.

[0077] A "physiologically effective amount" of an active substance indicates an adequate amount of the active substances to have a significant, externally observable effect on the patient. Thus, such a physiologically effective amount affects one or more of the characteristics in the patient without the need for special equipment to determine the effect. For example, a physiologically effective amount of a compound of the present invention has a significant, externally observable effect on the behavior of the patient by reducing one or more of the symptoms of autism or other pervasive developmental disorder. Accordingly, one

can determine whether an adequate amount of the active substance has been administered by watching the patient and observing whether changes have occurred in the patient due to the active substance.

[0078] 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 one embodiment, 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. Examples of inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Examples of 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. Examples of 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. Examples of 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.

[0079] The invention also includes all stereoisomers of the compounds, including diastereomers and enantiomers. The invention also includes mixtures of 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.

[0080] The compounds can be administered in prodrug form. Prodrugs are derivatives of the compounds, which are themselves relatively inactive but which convert into the active compound when introduced into the subject in which they are used by a chemical or biological process in vivo, such as an enzymatic conversion. Suitable prodrug formulations include, but are not limited to, peptide conjugates of the compounds of the invention and esters of compounds of the inventions. Further discussion of suitable prodrugs is provided in H. Bundgaard, *Design of Prodrugs*, New York: Elsevier, 1985; in R. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Boston: Elsevier, 2004; in R.L. Juliano (ed.), *Biological Approaches to the Controlled Delivery of Drugs* (Annals of the New York Academy of Sciences, v. 507), New York: New York Academy of Sciences, 1987; and in E.B. Roche (ed.), *Design of Biopharmaceutical Properties Through Prodrugs and Analogs* (Symposium sponsored by Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, November 1976 national meeting, Orlando, Florida), Washington : The Academy, 1977.

[0081] Metabolites of the compounds are also embraced by the invention.

[0082] "C_1-C_6 alkyl" is intended to embrace a saturated linear, branched, cyclic, or a combination thereof, hydrocarbon of 1 to 6 carbon atoms. Examples of "C_1-C_6 alkyl" are methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, cyclopropyl-methyl, methyl-cyclopropyl, pentyl, cyclopentyl, hexyl, and cyclohexyl, where the point of attachment of the alkyl group to the remainder of the molecule can be at any chemically possible location on the alkyl fragment. "C_1-C_4 alkyl" is intended to embrace a saturated linear, branched, cyclic, or a combination thereof, hydrocarbon of 1 to 4 carbon atoms. Examples of "C_1-C_4 alkyl" are methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl.

[0083] "Halogen" or "halo" designates fluoro, chloro, bromo, and iodo.

[0084] "C_1-C_6 haloalkyl" is intended to embrace any C_1-C_6 alkyl substituent having at least one halogen substituent; the halogen can be attached via any valence on the C_1-C_6 alkyl group. Some examples of C_1-C_6 haloalkyl are $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CH_2F$, $-CH_2Cl$.

[0085] In a first aspect, the present invention provides redox-active compositions that are able to reduce the symptoms of Pervasive Developmental Disorder (PDD), including of Autistic Disorder, Asperger's syndrome, Childhood Disintegrative Disorder (CDD), Rett's Disorder, and PDD-not otherwise specified (PDD-NOS) or attention deficit/hyperactivity disorder (ADHD) in a human patient. For example, the compositions are able to reduce or improve one or more symptoms, such as increased eye contact, better enunciation and use of pronouns, less fatigue, fewer tantrums, better sleep patterns, improved politeness and coordination, and increased voice and word association. In other words, the compositions are able to produce an adequate reduction of one or more of the observable characteristics of autism by an amount that is observable to a human observer, such as a parent, physician or caretaker, without the use of special devices such as microscopes or chemical analytical devices. The compositions reduce such symptoms by providing a physiologically effective amount of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd, and at least one of the group consisting of a physiologically acceptable carrier, adjuvant, excipient, buffer and diluent, which terms are used in their ordinary sense to indicate substances that assist in the packaging, delivery, absorption, or the physiological effect of the compounds. The physiologically acceptable carriers, adjuvants, excipients, buffers and diluents are preferably nontoxic to recipients at the dosages and concentrations employed. Representative samples include water, isotonic saline solutions that are preferably buffered at physiological pH (such as phosphate-buffered saline or Tris-buffered saline), mannitol, dextrose, glycerol, and ethanol, as well as selected polypeptides or proteins such as human serum albumin, maltodextrin, L-lysine, lactase and other carbohydratases, lipase and non-specific proteases such as papain. The carrier, adjuvant, excipient, buffer, or diluent may be combined with the compositions disclosed herein to provide compositions either as liquid solutions or, preferably, in solid form. For example, when the compositions are to be administered orally, the compositions may be produced in any of powder, tablet or capsule form.

Synthesis of Compounds

[0086] The compounds of the present invention can be readily synthesized by a variety of methods known in the art. The synthesis of alpha-tocopherol quinone is detailed in several references, for example in U.S.Pat. No. 3,406,188 and U.S.Pat. No 4,310,465. The synthesis of benzoquinone type compounds of the present invention is disclosed in co-owned US Patent Application Publication Nos. 2006/0281809, 2007/0072943, and 2007/0225261.

Clinical assessment of Autism

[0087] *Carnitine Deficiency*: As documented by Filipek, PA et al, in J, *Autism Dev. Diosrd.* (2004) 34:615-23 serum carnitine levels on 100 children with autism were investigated, concurrently with serum pyruvate, lactate, ammonia, and alanine levels. Values of free and total carnitine ($p < 0.001$), and pyruvate ($p = 0.006$) were significantly reduced while ammonia and alanine levels were considerably elevated ($p < 0.001$) in the autistic subjects. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, would suggest that assessing pyruvate, lactate, carnitine and ammonia levels may be useful when measured during routine evaluation of ASD children.

[0088] *Lactic acid (lactate) levels*: Some cases of autism have been associated with abnormal levels of lactic acid, as pyruvate levels increase and pyruvate is converted to lactate to maintain capacity for glycolysis (see Coleman, M. et al. *Journal of Autism and Developmental Disorders* (1985) 15, 1-8.) 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. 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).

[0089] *Lipid Peroxidation*: Lipid peroxidation has been found to be elevated in autism indicating that oxidative stress is increased in this disease. Lipid peroxidation can be measured by quantifying the levels of malonyldialdehyde (MDA), an end product of fatty acid oxidation. Several assays exist for MDA in plasma, urine, and other specimens. Such assays include specific reagents for UV detection by HPLC (Steghens, J. P., *et al.*, *Free Radic Biol Med* (2001) 31:242 and Pilz, J. *Chromatogr B Biomed Sci appl* (2000) 742:315 and capillary electrophoresis (Korizis, K. N. *et al.*, *Biomed Chromatogr* 15:287 (2001)). A

variety of lipid peroxidation products including MDA can be quantified using the thiobarbituric acid reaction (K Fukanaga *et al.*, *Biomed Chromatogr* (1998)12:300).

[0090] Lipid peroxidation can also be quantified by measurement of urinary levels of isoprostane F(2α)-VI, a marker of lipid peroxidation; 2,3-dinor-thromboxane B(2), which reflects platelet activation; and 6-keto-prostaglandin F(1α), a marker of endothelium activation, by means of gas chromatography-mass spectrometry in subjects with autism and healthy control subjects. Methods of detecting oxidant stress-related products are likewise known in the art. For example, enzyme immunoassay kits are commercially available from Cayman Chemical for determination of isoprostane F(2α)-VI (Cayman Chemical cat. no. 516301); for 2,3-dinor-thromboxane B(2) (Cayman Chemical cat. no. 519051), and for 6-keto-prostaglandin F(1α) (Cayman Chemical cat. no. 5152111).

[0091] *Antioxidant Proteins*: Levels of major antioxidant proteins, namely transferrin (iron–binding protein) and ceruloplasmin (copper–binding protein) in the serum, are significantly reduced in autistic children as compared to their developmentally normal non-autistic siblings. A striking correlation was observed between reduced levels of these proteins and loss of previously acquired language skills in children with autism. These results indicate that altered regulation of transferrin and ceruloplasmin in autistic children who lose acquired language skills can be used for diagnosis of disease during evaluation of patients.

[0092] In one embodiment, the invention also embraces modulating one or more autism biomarkers, normalizing one or more autism biomarkers, or enhancing one or more autism biomarkers, comprising administering to a subject a therapeutically effective amount or physiologically effective amount of one or more compounds or compositions as described herein. The invention also embraces compounds and compositions as described herein, which are useful for modulating one or more autism biomarkers, normalizing one or more autism biomarkers, or enhancing one or more autism biomarkers.

[0093] "Autism biomarkers" include free carnitine levels, total carnitine levels, pyruvate levels, ammonia levels, alanine levels, lactate levels, malonyldialdehyde (MDA) levels, isoprostane F(2α)-VI levels, 2,3-dinor-thromboxane B(2) levels, 6-keto-prostaglandin F(1α) levels, transferrin levels and ceruloplasmin levels. These biomarkers can be measured in whole blood, serum, plasma, urine, cerebrospinal fluid, cerebral ventricular fluid, or any other biological samples, bodily fluids, or body compartments.

[0094] The compounds and compositions of the invention can be used in subjects or patients to modulate one or more autism biomarkers. Modulation of autism biomarkers can be done to normalize autism biomarkers in a subject, or to enhance autism biomarkers in a subject.

[0095] Normalization of one or more autism biomarkers is defined as either restoring the level of one or more such autism biomarkers to normal or near-normal levels in a subject whose levels of one or more autism biomarkers show pathological differences from normal levels (i.e., levels in a healthy subject), or to change the levels of one or more autism biomarkers to alleviate pathological symptoms in a subject. Depending on the nature of the autism biomarker, such levels may show measured values either above or below values in non-autistic subjects. For example, carnitine levels are sometimes reduced in autistic subjects in comparison to non-autistic subjects, and an increase in the carnitine level may be desirable. Ammonia levels are sometimes higher in autistic subjects in comparison to non-autistic subjects, and a decrease in ammonia levels may be desirable. Normalization of autism biomarkers can involve restoring the level of autism biomarkers of an autistic subject to within about at least two standard deviations of the non-autistic value, more preferably to within about at least one standard deviation of the non-autistic value, to within about at least one-half standard deviation of the non-autistic value, or to within about at least one-quarter standard deviation of the non-autistic value.

[0096] When an increase in an autism biomarker level is desired to normalize the one or more such autism biomarkers, the level of the autism biomarker in an autistic subject can be increased to within about at least two standard deviations of the value in a non-autistic subject, more preferably increased to within about at least one standard deviation of the non-autistic value, increased to within about at least one-half standard deviation of the non-autistic value, or increased to within about at least one-quarter standard deviation of the non-autistic value, by administration of one or more compounds or compositions according to the invention. Alternatively, the level of one or more of the autism biomarkers can be increased by about at least 10% above the subject's level of the respective one or more autism biomarkers before administration, by about at least 20% above the subject's level of the respective one or more autism biomarkers before administration, by about at least 30% above the subject's level of the respective one or more autism biomarkers before administration, by about at least 40% above the subject's level of the respective one or more autism biomarkers

before administration, by about at least 50% above the subject's level of the respective one or more autism biomarkers before administration, by about at least 75% above the subject's level of the respective one or more autism biomarkers before administration, or by about at least 100% above the subject's level of the respective one or more autism biomarkers before administration.

[0097] When a decrease in a level of one or more autism biomarkers is desired to normalize the one or more autism biomarkers, the level of the one or more autism biomarkers in an autistic subject can be decreased to a level within about at least two standard deviations of the value in a non-autistic subject, more preferably decreased to within about at least one standard deviation of the value in a non-autistic subject, decreased to within about at least one-half standard deviation of the value in a non-autistic subject, or decreased to within about at least one-quarter standard deviation of the value in a non-autistic subject, by administration of one or more compounds or compositions according to the invention. Alternatively, the level of the one or more autism biomarkers can be decreased by about at least 10% below the subject's level of the respective one or more autism biomarkers before administration, by about at least 20% below the subject's level of the respective one or more autism biomarkers before administration, by about at least 30% below the subject's level of the respective one or more autism biomarkers before administration, by about at least 40% below the subject's level of the respective one or more autism biomarkers before administration, by about at least 50% below the subject's level of the respective one or more autism biomarkers before administration, by about at least 75% below the subject's level of the respective one or more autism biomarkers before administration, or by about at least 90% below the subject's level of the respective one or more autism biomarkers before administration.

[0098] Enhancement of the level of one or more autism biomarkers is defined as changing the extant levels of one or more autism biomarkers in an autistic subject to a level which provides beneficial or desired effects for the subject. Additional enhancement, beyond normalization, may be necessary in the event that normalizing the level of one or more autism biomarkers does not suffice to bring about an improvement in symptoms.

[0099] Accordingly, when an increase in a level of one or more autism biomarkers is beneficial to an autistic subject, enhancement of the one or more autism biomarkers can involve increasing the level of the respective autism biomarker or autism biomarkers in the autistic subject to about at least one-quarter standard deviation above the value in a non-

autistic subject, about at least one-half standard deviation above the value in a non-autistic subject, about at least one standard deviation above the value in a non-autistic subject, or about at least two standard deviations above the value in a non-autistic subject. Alternatively, the level of the one or more autism biomarkers can be increased by about at least 10% above the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 20% above the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 30% above the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 40% above the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 50% above the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 75% above the subject's level of the respective one or more autism biomarkers before enhancement, or by about at least 100% above the subject's level of the respective one or more autism biomarkers before enhancement.

[0100] When a decrease in a level of one or more autism biomarkers is desired to enhance one or more autism biomarkers, the level of the one or more autism biomarkers in an autistic subject can be decreased by an amount of about at least one-quarter standard deviation of the value in a non-autistic subject, decreased by about at least one-half standard deviation of the value in a non-autistic subject, decreased by about at least one standard deviation of the value in a non-autistic subject, or decreased by about at least two standard deviations of the value in a non-autistic subject. Alternatively, the level of the one or more autism biomarkers can be decreased by about at least 10% below the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 20% below the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 30% below the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 40% below the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 50% below the subject's level of the respective one or more autism biomarkers before enhancement, by about at least 75% below the subject's level of the respective one or more autism biomarkers before enhancement, or by about at least 90% below the subject's level of the respective one or more autism biomarkers before enhancement.

Pharmaceutical, nutraceutical and nutritional formulations

[0101] 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, or as nutraceutical or nutritional formulations with additives such as nutraceutically or nutritionally acceptable excipients, nutraceutically or nutritionally acceptable carriers, and nutraceutically or nutritionally acceptable vehicles.

[0102] Suitable pharmaceutically acceptable excipients, carriers and vehicles include processing agents and drug delivery modifiers and enhancers, such as, for example, 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.

[0103] A pharmaceutical composition can comprise a unit dose formulation, where the unit dose is a dose sufficient to have a therapeutic or suppressive effect. The unit dose may be sufficient as a single dose to have a therapeutic or suppressive effect. Alternatively, the unit dose may be a dose administered periodically in a course of treatment or suppression of a disorder. A unit dose can contain a therapeutically effective amount of a composition disclosed herein. Alternatively, a unit dose can contain a physiologically effective amount of a composition disclosed herein.

[0104] Pharmaceutical compositions containing the compounds of the invention may be in any form suitable for the intended method of administration, including, for example, 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 of the present invention include, for example, 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, for example, monohydric alcohols, such as ethanol, and polyhydric alcohols, such as glycols. Suitable oils include, for example, 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 of the present invention may also be in the form of microparticles, microcapsules, liposomal encapsulates, and the like, as well as combinations of any two or more thereof.

[0105] The compositions, as described above, can be prepared as nutritional formulations such as foods, including medical or functional foods and dietary supplements. A "medical or functional food" is defined as being consumed as part of a usual diet but which has been demonstrated to have physiological benefits and/or to reduce the risk of chronic disease, beyond basic nutritional functions. A "dietary supplement" is defined as a product that is intended to supplement the human diet and is typically provided in the form of a pill, capsule, tablet, or like formulation. By way of example, but not limitation, a dietary supplement may include one or more of the following ingredients: vitamins, minerals, herbs, botanicals, amino acids, dietary substances intended to supplement the diet by increasing total dietary intake, and concentrates, metabolites, constituents, extracts or combinations of any of the foregoing. Dietary supplements may also be incorporated into food stuffs, such as functional foods designed to promote health or to prevent disease or disorders. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient in any of a number of methods. The subject compositions may be administered alone or in combination with other pharmaceutical agents and can be combined with a physiologically acceptable carrier thereof. The effective amount and method of administration of the particular formulation can vary based on the individual subject, the stage of disease, and other factors evident to one skilled in the art. During the course of the treatment, the concentration of the subject compositions may be monitored (for example, blood plasma levels may be monitored) to insure that the desired level is maintained.

[0106] The term "nutraceutical" has been used to refer to any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease. Hence, compositions falling under the label "nutraceutical" may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer

foods, herbal products, and processed foods such as cereals, soups and beverages. In a more technical sense, the term has been used to refer to a product isolated or purified from foods, and generally sold in medicinal forms not usually associated with food and demonstrated to have a physiological benefit or provide protection against chronic disease. Suitable nutraceutically acceptable excipients may include liquid solutions such as a solution comprising a vegetable- and/or animal- and/or fish-derived oil.

[0107] 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, for example, a biodegradable material that can degrade spontaneously *in situ* and *in vivo* for, example, by hydrolysis or enzymatic cleavage, *e.g.*, by proteases. The delivery system may be, for example, a naturally occurring or synthetic polymer or copolymer, for example 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).

[0108] The compounds of the invention may be administered enterally, orally, parenterally, buccally, sublingually, by inhalation (e.g. as mists or sprays), rectally, vaginally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. For example, suitable modes of administration include oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intraarterial, intramuscular, intraocular, intraperitoneal, intranasal (e.g. via nasal mucosa), 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, intrasternal 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 effective. Additional methods of administration are known in the art.

[0109] Injectable preparations, for example, 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, for example, 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 di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0110] 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.

[0111] 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.

[0112] The compounds of the present invention 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 multi-lamellar 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 of the present invention, 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).

[0113] In a preferred embodiment, the compositions are provided to the patient as either a food or a food supplement. For example, when provided as a food the compositions of the present invention are combined with material primarily made up of protein, carbohydrate and/or fat that is used in the body, preferably a human body, to sustain growth, repair, and vital processes, and to furnish energy. When provided as a food supplement, the compositions comprise selected substances such that they can be eaten at or about the same time as a food. The food supplements are generally eaten within about one hour before or after the food is eaten, typically within about one-half hour before or after the food is eaten, preferably within about 15 minutes of when the food is eaten, and further preferably within one to five minutes of the time the food is eaten. The food supplement can also be eaten at the same time as the food, or even with the food.

[0114] The invention also provides articles of manufacture and kits containing materials useful for treating or suppressing PDD including Autism or for reducing the symptoms of one or more symptoms of PDD. The invention also provides kits comprising any one or more of the compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd, or mixtures thereof. In some embodiments, the kit of the invention comprises the container described above.

[0115] In other aspects, the kits may be used for any of the methods described herein, including, for example, to treat an individual with a pervasive developmental disorder,

including an autistic spectrum disorder, or to suppress a pervasive developmental disorder, such as an autistic spectrum disorder in an individual.

[0116] In other aspects, the kits may be used for any of the methods described herein, including, for example, to treat an individual with an attention deficit disorder, including attention deficit/hyperactivity disorder (ADHD), or to suppress an attention deficit disorder, such as attention deficit/hyperactivity disorder (ADHD) in an individual.

[0117] 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 physiologically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0118] Examples of dosages which can be used are an 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 of the present invention 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.

[0119] While the compounds of the invention 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. If compounds are administered together, they need not be administered by the same route, or in the same formulation. However, they can be combined into one formulation as desired.

[0120] Representative agents useful in combination with the compounds of the invention for the treatment or suppression of PDD, ASD, or ADHD symptoms include, but are not limited to, Coenzyme Q10 and antioxidant compounds and/or drugs, such as but not limited to carnitine, quercetine, mangosteen, acai, uridine, N-acetyl cysteine (NAC), vitamin A, vitamin C, lutein, beta-carotene, lycopene, and glutathione. Other agents useful in combination with the compounds of the invention are compounds and/or drugs that have an effect on the neurotransmitters, particularly serotonin and dopamine, that include antidepressants, anti-anxiety drugs, antispasmodics, neuroleptics and atypical neuroleptics, and stimulants. Antidepressants include but are not limited to Selective Serotonin Reuptake Inhibitors (SSRIs) (fluoxetine (Prozac); fluvoxamine (Luvox); paroxetine (Paxil); sertraline (Zoloft); citalopram (Celexa)); Tricyclic antidepressants (amitriptyline (Elavil); amitriptyline/chlordiazepoxide (Limbitrol); amoxapine (Asendin); clomipramine (Anafranil); desipramine (Norpramin); doxepin (Sinequan); imipramine (Tofranil); nortriptyline (Avenytl, Pamelor); protriptyline (Vivactil); trimipramine (Surmontil)); MAO Inhibitors (moclobemide (Aurorex); phenelzine (Nardil); tranylcypromine sulfate (Parnate)); Buproprion; Lithium; Mirtazapine; Nefazodone (Serzone); Reboxetine (Edronax); Venlafaxine (Effexor, Effexor XR); and "natural" anti-depressants such as St. John's Wart. Anti-anxiety drugs include but are not limited to alprazolam (Xanax); chlordiazepoxide (Librium); clonazepam (Klonopin); clorazepate (Tranxene); diazepam (Valium); lorazepam (Ativan); oxazepam (Serax); and prazepam (Centrax). Antispasmodic medications include but are not limited to carmazepine (Tegretol); clonazepam (Klonopin); ethosuximide (Zarontin); ethotoin (Peganone); fosphenytoin (Cerebyx); gabapentin (Neurontin); lamotrigine (Lamictal); mephenytoin (Mesantoin); phenobarbital (Luminol, Solfoton); phenytoin (Dilantin); primidone (Mysoline); toiramate (Topamax); valproic acid (Depakene); divalproex sodium (Depakote, Depakote Sprinkles); and Gabapentin (Neurontin). Stimulants include but are not limited to dextroamphetamine sulfate (Das, Dexampex, Dexedrine, Dexedrine Spansules, Dextrostat, Ferndex, Oxydess); dextroamphetamine/amphetamine (Adderall); methamphetamine (MTH); methylphenidate hydrochloride (Ritalin); and pemoline (Cyclert); and phenylpropanolamine (PPA). Atypical neuroleptics include but are not limited to clozapine (Clozaril); olanzapine (Zyprexa); risperidone (Risperdal); quetiapine (Seroquel); and ziprasidone (Zeldox).

[0121] The compounds of the invention can be administered in combination with one or more minerals, such as, but not limited to, iron, calcium, potassium, zinc, manganese, phosphorous, chromium, magnesium, manganese, molybdenum, tin, nickel, sulfur, selenium, copper, cobalt, chloride, fluoride, and iodine. The minerals may be administered in large or trace amounts. The compounds can be administered together with the minerals in one formulation, or in different formulations.

[0122] When additional active agents are used in combination with the compounds of the present invention, 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 useful amounts as would be known to one of ordinary skill in the art.

[0123] The compounds of the invention 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 of the invention 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.

[0124] The invention will be further understood by the following non-limiting example.

Example

Screening Compounds of the Invention in Human Dermal Fibroblasts from Autistic Patients

[0125] A screen was performed to identify compounds effective for the amelioration of ASD. Test samples, and solvent controls were tested for their ability to rescue ASD fibroblasts stressed by addition of L-buthionine-(S,R)-sulfoximine (BSO).

[0126] MEM (a medium enriched in amino acids and vitamins, catalog no. Gibco 11965) and Fetal Calf Serum were obtained from Invitrogen. Basic fibroblast growth factor and epidermal growth factor were purchased from PeproTech. Penicillin-streptomycin-glutamine mix, L-buthionine (S,R)-sulfoximine, and insulin from bovine pancreas were purchased from Sigma. Calcein AM was purchased from Molecular Probes. Cell culture medium (ATP) was made by combining 75 ml Fetal Calf Serum, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine, 10 ng/ml EGF, and 10 ng/ml bFGF; MEM EBS was added to make the

volume up to 500 ml. A 10 mM BSO solution was prepared by dissolving 444 mg BSO in 200 ml of medium with subsequent filter-sterilization. During the course of the experiments, this solution was stored at +4°C. The cells were obtained from Dr. J.M. Shoffner , Medical Neurogenetics, Atlanta, GA and were grown in 10 cm tissue culture plates. Every week, they were split at a 1:3 ratio.

[0127] The samples were supplied in 1.5 ml glass vials. The compounds were diluted with DMSO, ethanol or PBS to result in a 5 mM stock solution. Once dissolved, they were stored at -20°C.

[0128] The samples were screened according to the following protocol:
A culture with ASD fibroblasts was started from a 1 ml vial with approximately 500,000 cells stored in liquid nitrogen. Cells were propagated in 10 cm cell culture dishes by splitting every week in a ratio of 1:3 until nine plates were available. Once confluent, fibroblasts were harvested. For 54 micro titer plates (96 well-MTP) a total of 14.3 million cells (passage eight) were re-suspended in 480 ml medium, corresponding to 100 µl medium with 3,000 cells/well. The remaining cells were distributed in 10 cm cell culture plates (500,000 cells/plate) for propagation. The plates were incubated overnight at 37°C in an atmosphere with 95% humidity and 5% CO_2 to allow attachment of the cells to the culture plate.

[0129] MTP medium (243 µl) was added to a well of the microtiter plate. The test compounds were unfrozen, and 7.5 µl of a 5 mM stock solution was dissolved in the well containing 243 µl medium, resulting in a 150 µM master solution. Serial dilutions from the master solution were made. The period between the single dilution steps was kept as short as possible (generally less than 1 second).

[0130] Plates were kept overnight in the cell culture incubator. The next day, 10 µl of a 10 mM BSO solution were added to the wells, resulting in a 1 mM final BSO concentration. Forty-eight hours later, three plates were examined under a phase-contrast microscope to verify that the cells in the 0% control (wells E1-H1) were clearly dead. The medium from all plates was discarded, and the remaining liquid was removed by gently tapping the plate inversed onto a paper towel.

[0131] 100 µl of PBS containing 1.2 µM Calcein AM were then added to each well. The plates were incubated for 50-70 minutes at room temperature. After that time the PBS was

discarded, the plate gently tapped on a paper towel and fluorescence (excitation/emission wavelengths of 485 nm and 525 nm, respectively) was read on a Gemini fluorescence reader. Data was imported into Microsoft Excel (EXCEL is a registered trademark of Microsoft Corporation for a spreadsheet program) and used to calculate the EC_{50} concentration for each compound.

[0132] The compounds were tested three times, i.e., the experiment was performed three times, the passage number of the cells increasing by one with every repetition.

[0133] The solvents (DMSO, ethanol, PBS) neither had a detrimental effect on the viability of non-BSO treated cells nor did they have a beneficial influence on BSO-treated fibroblasts even at the highest concentration tested (1%). None of the compounds showed auto-fluorescence. The viability of non-BSO treated fibroblasts was set as 100%, and the viability of the BSO- and compound-treated cells was calculated as relative to this value.

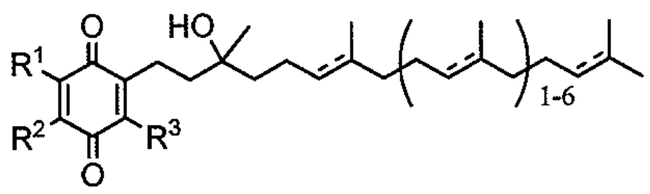
[0134] Certain compounds of the present invention such as: 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione and 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione exhibited protection against ASD with an EC_{50} of less than about 150 nM.

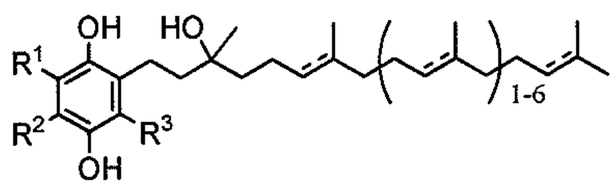
[0135] In general, the nomenclature used in this Application was generated with the help of naming package within the ChemOffice.RTM. version 11.0 suite of programs by CambridgeSoft Corp (Cambridge, Mass.).

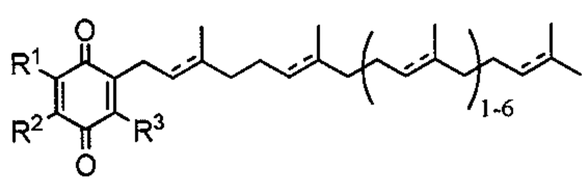
CLAIMS

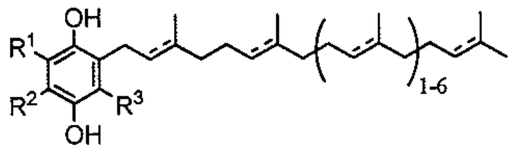
What is claimed is:

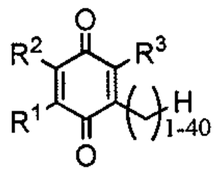
1. A composition for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) or attention deficit/hyperactivity disorder (ADHD) , in a patient in need of such treatment comprising one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI or mixtures thereof,

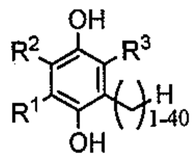

(I)


(II)


(III)


(IV)


(V)


(VI)

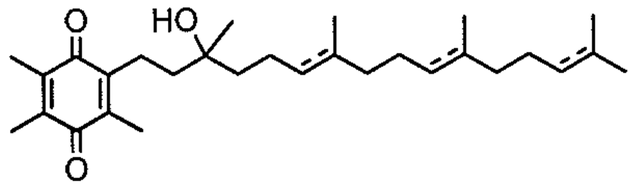
wherein,

the bonds indicated with a dashed line are all single bonds or are all double bonds;

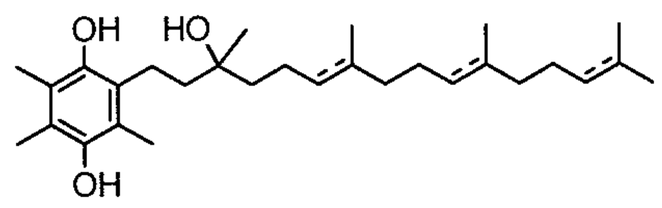
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

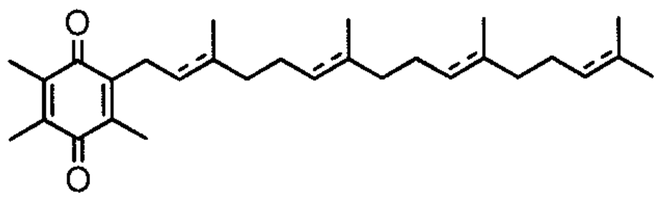
2. The composition according to claim 1, comprising one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,



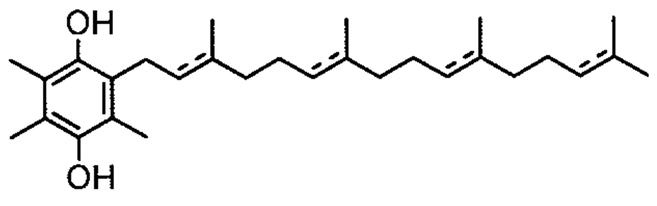
(Ia)



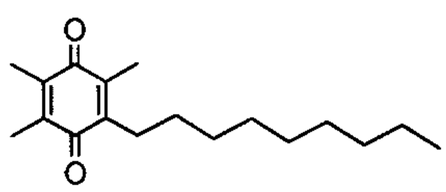
(IIa)



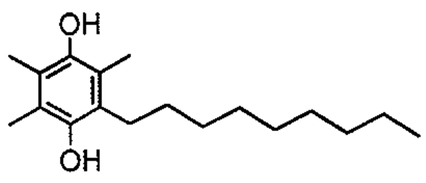
(IIIa)



(IVa)



(Va)



(VIa)

or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

3. The composition according to claim 2, wherein the compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); 2-((3R,6E,10E)-3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10-dienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib-R); 2-((3S,6E,10E)-3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10-dienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib-S); 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); 2-((3R,7R,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-RRR); 2-((3S,7R,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-SRR); 2-((3R,7S,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-RSR); 2-((3R,7R,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-RRS); 2-((3S,7S,11R)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-SSR); 2-((3S,7R,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-SRS); 2-((3R,7S,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-RSS); 2-((3S,7S,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic-SSS); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); 2,3,5-trimethyl-6-((3R,7R,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-RRR); 2,3,5-trimethyl-6-((3S,7R,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-SRR); 2,3,5-trimethyl-6-((3R,7S,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-RSR); 2,3,5-trimethyl-6-((3R,7R,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-RRS); 2,3,5-trimethyl-6-((3S,7S,11R)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-SSR); 2,3,5-trimethyl-6-((3S,7R,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-SRS); 2,3,5-trimethyl-6-((3R,7S,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-RSS); 2,3,5-trimethyl-6-((3S,7S,11S)-3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc-SSS); or 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

4. The composition according to claim 1, wherein said composition is for reducing the symptoms associated with, or for treating or suppressing autistic spectrum disorder (ASD).

5. The composition according to claim 2, wherein said composition is for reducing the symptoms associated with, or for treating or suppressing autistic spectrum disorder (ASD).

6. The composition according to claim 4, wherein the compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; or 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

7. The composition according to claim 1, wherein said composition is for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).

8. The composition according to claim 2, wherein said composition is for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).

9. The composition according to claim 8, wherein the compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; or 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

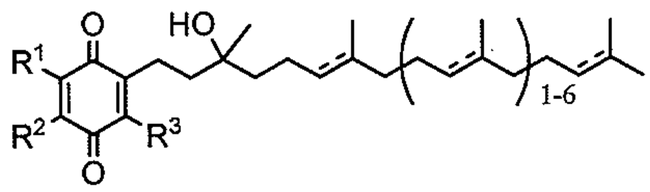
10. A medical food, a functional food, a food supplement, or a dietary supplement for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) or attention deficit/hyperactivity disorder (ADHD), in a patient in need of such treatment; comprising compositions of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, Formula Ib, Formula Ib-R, Formula Ib-S, Formula Ic, Formula Ic-RRR, Formula Ic-SRR, Formula Ic-RSR, Formula Ic-RRS, Formula Ic-SSR, Formula Ic-SRS, Formula Ic-RSS, Formula Ic-SSS, Formula IIIb, Formula IIIc, Formula IIIc-RRR, Formula IIIc-SRR, Formula IIIc-RSR, Formula IIIc-RRS, Formula IIIc-SSR, Formula IIIc-SRS, Formula IIIc-RSS, Formula IIIc-SSS, Formula Id, Formula IId, Formula IIId, or Formula IVd, and at least one of the group consisting of a physiologically or nutritionally acceptable carrier, adjuvant, excipient, buffer and diluent.

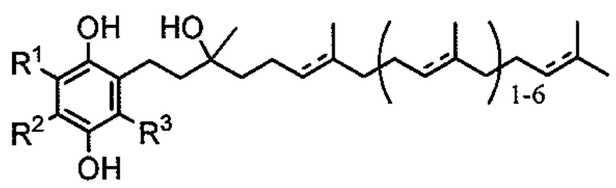
11. The medical food, functional food, food supplement or dietary supplement according to claim 10, wherein the compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; or 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

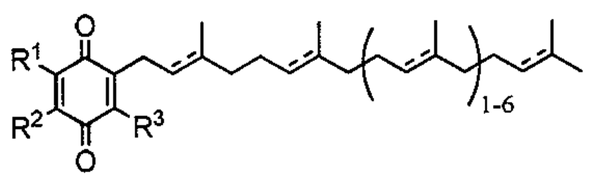
12. The medical food, functional food, food supplement or dietary supplement according to claim 10, for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) selected from autistic spectrum disorder (ASD).

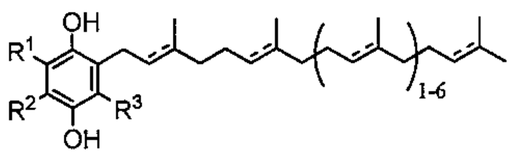
13. The medical food, functional food, food supplement or dietary supplement according to claim 10, for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).

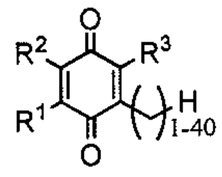
14. A method of reducing the symptoms associated with, or of treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment by administering a therapeutically or physiologically effective amount of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, or mixtures thereof,

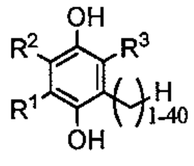

(I)


(II)


(III)


(IV)


(V)


(VI)

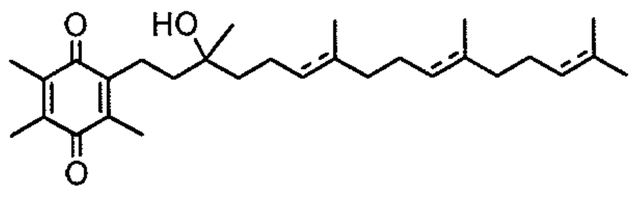
wherein,

the bonds indicated with a dashed line are all single bonds or are all double bonds;

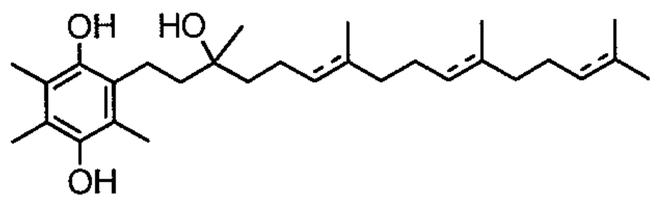
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

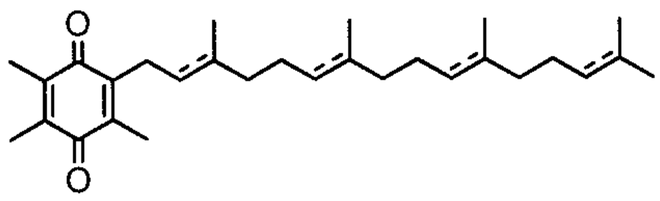
15. The method according to claim 14, comprising administering a therapeutically or physiologically effective amount of one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,



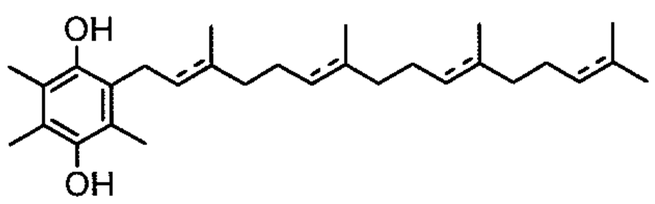
(Ia)



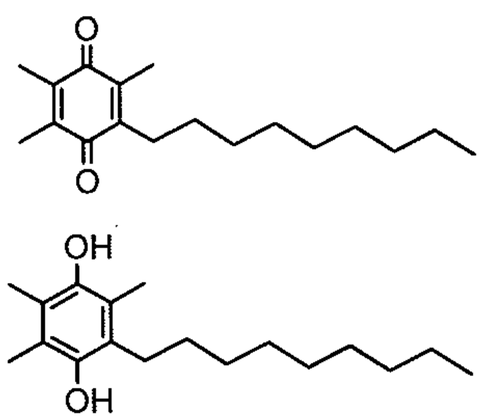
(IIa)



(IIIa)



(IVa)



(Va)

(VIa)

or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof,
for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment.

16. The method according to claim 15 for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment, wherein the administered compound is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; or 2,3,5-trimethyl-6-

nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof.

17. The method according to claim 14, wherein the Pervasive Developmental Disorder (PDD) is autistic spectrum disorder (ASD).

18. The method according to claim 15, wherein the Pervasive Developmental Disorder (PDD) is autistic spectrum disorder (ASD).

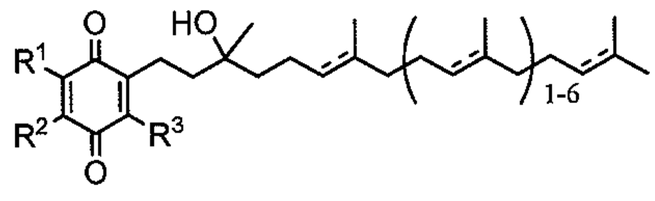
19. The method according to claim 16, wherein the Pervasive Developmental Disorder (PDD) is autistic spectrum disorder (ASD).

20. The method according to claim 14, wherein the disorder is attention deficit/hyperactivity disorder (ADHD).

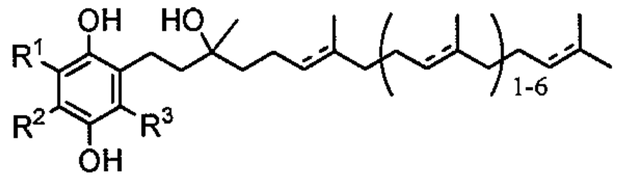
21. The method according to claim 15, wherein the disorder is attention deficit/hyperactivity disorder (ADHD).

22. The method according to claim 16, wherein the disorder is attention deficit/hyperactivity disorder (ADHD).

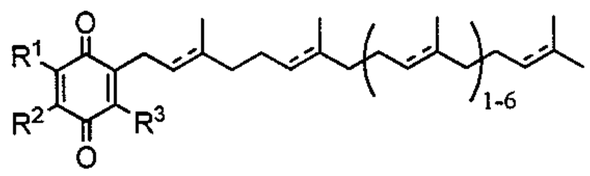
23. Use of one or more compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, or mixtures thereof,



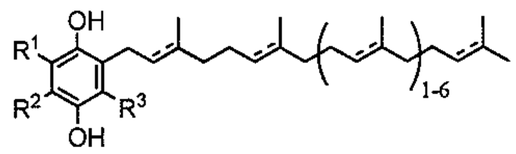
(I)

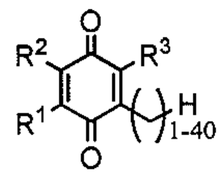


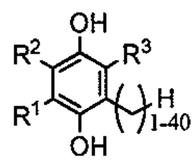
(II)



(III)


(IV)


(V)


(VI)

wherein,

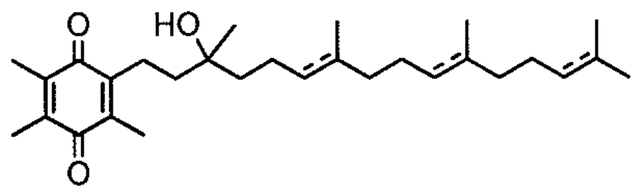
the bonds indicated with a dashed line are all single bonds or are all double bonds;

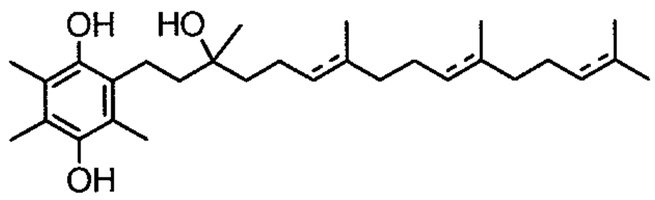
R^1, R^2, and R^3 are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, halogen and CN;

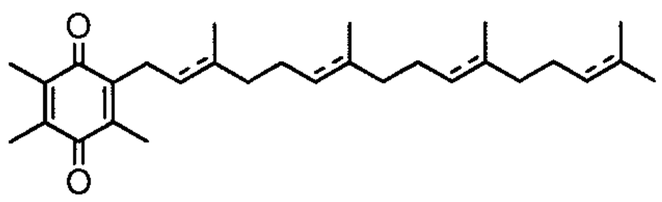
or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof;

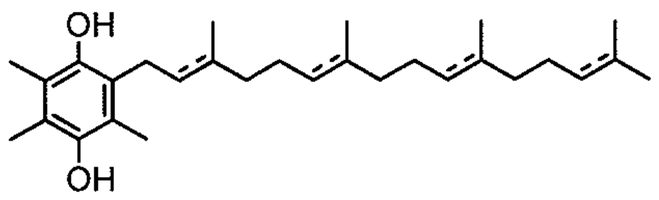
for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment.

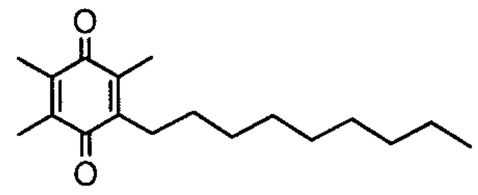
24. The use according to claim 23, of one or more compounds of Formula Ia, Formula IIa, Formula IIIa, Formula IVa, Formula Va, Formula VIa, or mixtures thereof,


(Ia)

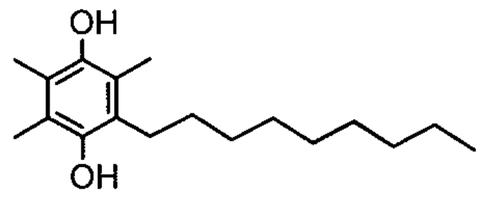

(IIa)


(IIIa)


(IVa)



(Va)



(VIa)

or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof;

for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment.

25. The use according to claim 23, of one or more compounds selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ib); Ib-R; Ib-S; 2-(3-hydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (Ic); Ic-RRR; Ic-SRR; Ic-RSR; Ic-RRS; Ic-SSR; Ic-SRS; Ic-RSS; Ic-SSS; 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl)cyclohexa-2,5-diene-1,4-dione (III-b); 2,3,5-trimethyl-6-(3,7,11,15-tetramethylhexadecyl)cyclohexa-2,5-diene-1,4-dione (IIIc); IIIc-RRR; IIIc-SRR; IIIc-RSR; IIIc-RRS; IIIc-SSR; IIIc-SRS; IIIc-RSS; IIIc-SSS; or 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione, or a stereoisomer, a mixture of stereoisomers, a solvate or a hydrate thereof; for reducing the symptoms associated with, or for treating or suppressing pervasive developmental disorders (PDDs) or attention deficit/hyperactivity disorder (ADHD) in a patient in need of such treatment.

26. The use according to claim 23, for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) selected from autistic spectrum disorder (ASD).

27. The use according to claim 24, for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) selected from autistic spectrum disorder (ASD).

28. The use according to claim 25, for reducing the symptoms associated with, or for treating or suppressing a pervasive developmental disorder (PDD) selected from autistic spectrum disorder (ASD).

29. The use according to claim 23, for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).

30. The use according to claim 24, for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).

31. The use according to claim 25, for reducing the symptoms associated with, or for treating or suppressing attention deficit/hyperactivity disorder (ADHD).