cholesterol has been shown to decrease the activities of beta- and gamma-secretases, blocking the pathogenic processing of beta-amyloid[15-16]. At the molecular level, cholesterol binds to the transmembrane domain of amyloid precursor protein (APP), activating the trafficking of APP to cholesterol-rich membrane domains rich in beta- and gamma-secretases, resulting in amyloid-beta production[17]. Synaptic membrane changes resulting from increased cholesterol may also be an important factor in the utilization of membrane phospholipids to support cholinergic neurotransmission (autocannibalism concept)[18]. Early utilization of statins have also been suggested to reduce the incidence or delay the onset of Alzheimer's and Parkinson's diseases[19]. Cholesterol accumulation also occurs in the drusen associated with age-related macular degeneration[20]. Membrane cholesterol is also increased in cancer[21] and increases in mitochondrial membrane cholesterol have been hypothesized to be the defect that leads to the Warburg effect that is associated with most cancer cells[22]. The Warburg effect is a defining feature of cancer cells in that, unlike normal cells, which rely almost entirely upon respiration for energy, cancer cells can utilize both respiration and glycolysis for energy.

In addition to complex negative membrane effects of cholesterol accumulation, there is also increased oxysterol production[23]. These oxysterols are cytotoxic (apoptosis and necrosis), pro-inflammatory, deplete GSH and induce phospholipidosis[23-26]. Diseases in which these toxic oxysterols might be involved include neurodegeneration (both neuronal and demyelinating), osteoporosis, age-related macular degeneration and cardiovascular diseases, particularly atherosclerosis[23].

Current clinical therapies to reduce cholesterol consist mainly of inhibiting cholesterol synthesis with statins or blocking cholesterol absorption from the gastrointestinal tract with ezetimibe. To the inventors' knowledge, there are currently no drugs to mobilize cholesterol trafficking out of membranes.

SUMMARY OF THE INVENTION

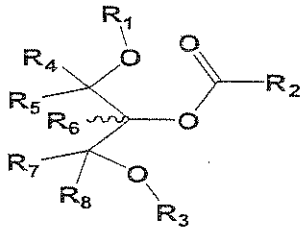
The present ~~invention~~disclosure relates to compounds and methods for treating diseases of aging associated with abnormal membrane cholesterol levels. The described compounds include novel plasmalogen precursors which decrease membrane free cholesterol levels and augment cholesterol esterification for transport from cell membranes. These compounds therefore are useful for reducing membrane cholesterol levels in subjects suffering from elevated membrane cholesterol levels. The compounds can also be used to treat or prevent diseases

associated with increased membrane cholesterol such as neurodegenerative diseases (including but not limited to Alzheimer's disease, Parkinson's disease, multiple sclerosis and age-related macular degeneration), cognitive impairment, dementia, cancers (including but not limited to prostate, lung, breast, ovarian, and kidney cancer), osteoporosis, bipolar disorder and vascular diseases (including but not limited to atherosclerosis and hypercholesterolemia). Furthermore, these compounds are useful in the treatment of disorders resulting from abnormal genetic expression of cholesterol transport proteins, such as apolipoprotein E.

These plasmalogen precursors contain a glycerol backbone with an alkyl or alkenyl lipid substitution at sn-1 and an acyl lipid substitution at sn-2. A polar substituent is provided at sn-3 to improve pharmaceutical properties (such as to improve stability and/or bioavailability, or for formulation as a salt).

Without wishing to be bound by theory, it is believed that in certain embodiments the sn-3 substituent is cleaved by lipases and the resulting 1-alkyl, 2-acyl glycerol or 1-alkenyl, 2-acyl glycerol is then converted to plasmalogens in the endoplasmic reticulum, thereby bypassing the peroxisomal compartment which can demonstrate decreased function with ageing.

In one aspect, there is provided a compound according to the structure of formula I:



(I)

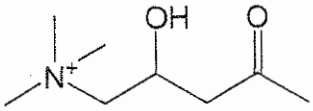
wherein:

R_1 and R_2 are the same or different and selected from an alkyl or alkenyl hydrocarbon chain selected from the group consisting of: $CH_3(CH_2)_3$-, $CH_3(CH_2)_5$-, $CH_3(CH_2)_7$-, $CH_3(CH_2)_9$-, $CH_3(CH_2)_{11}$-, $CH_3(CH_2)_{13}$-, $CH_3(CH_2)_{15}$-, $CH_3(CH_2)_{17}$-, $CH_3(CH_2)_{19}$-, $CH_3(CH_2)_{21}$-, $CH_3(CH_2)_{23}$-, $CH_3(CH_2)_3CH=CH(CH_2)_7$-, $CH_3(CH_2)_5CH=CH(CH_2)_7$-, $CH_3(CH_2)_7CH=CH(CH_2)_7$-, $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7$-, $CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7$-, $CH_3CH_2(CH=CH)$-, $CH_3(CH_2)_3(CH=CH)$-, $CH_3(CH_2)_5(CH=CH)$-, $CH_3(CH_2)_7(CH=CH)$-,

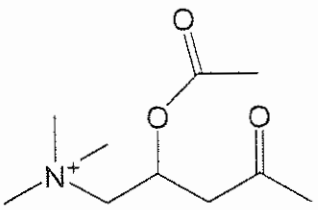
$CH_3(CH_2)_9(CH=CH)$-, $CH_3(CH_2)_{11}(CH=CH)$-, $CH_3(CH_2)_{13}(CH=CH)$-,
$CH_3(CH_2)_{15}(CH=CH)$-, $CH_3(CH_2)_{17}(CH=CH)$-, $CH_3(CH_2)_{19}(CH=CH)$-,
$CH_3(CH_2)_{21}(CH=CH)$-, $CH_3(CH_2)_3CH=CH(CH_2)_5(CH=CH)$-,
$CH_3(CH_2)_5CH=CH(CH_2)_5(CH=CH)$-, $CH_3(CH_2)_7CH=CH(CH_2)_5(CH=CH)$-,
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_5(CH=CH)$,
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_5(CH=CH)$-, $CH_3(CH_2)_3CH=CH(CH_2)_7$-,
$CH_3(CH_2)_5CH=CH(CH_2)_7$-, $CH_3(CH_2)_7CH=CH(CH_2)_7$-, $CH_3(CH_2)_4(CH=CHCH_2)_2(CH_2)_6$-,
$CH_3CH_2(CH=CHCH_2)_3(CH_2)_6$-, $CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2$-,
$CH_3CH_2(CH=CHCH_2)_5(CH_2)_2$-, $CH_3(CH_2)_7CH=CH(CH_2)_{11}$, and $CH_3CH_2(CH=CHCH_2)_6CH_2$-;

R_3 is selected from the group consisting of carnitine, acetyl-D/L-carnitine, thiocarnitine, acetyl-D/L-thiocarnitine, creatine, norcarnitine, lipoic acid, dihydrolipoic acid, N-acetylcysteine, substituted or unsubstituted amino acid groups and groups of the structures shown below:

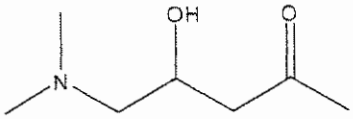
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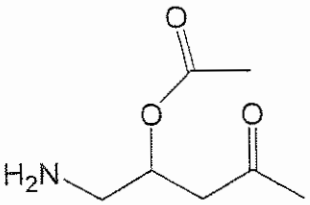
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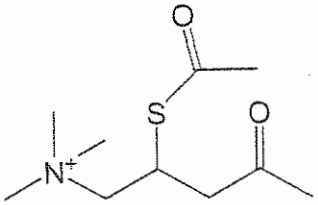
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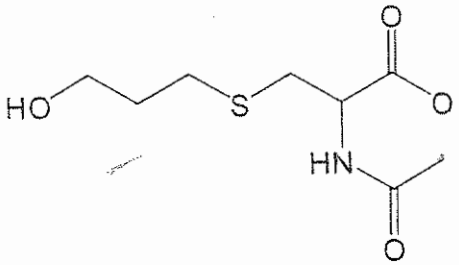
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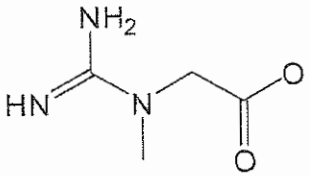
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8



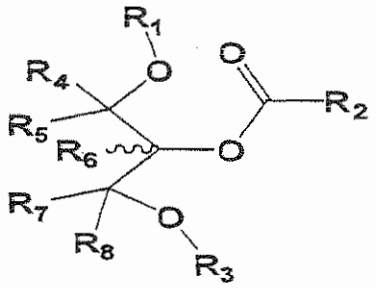
R_4 and R_5 are independently hydrogen or lower alkyl;

R_6 is hydrogen or lower alkyl; and

R_7 and R_8 are independently hydrogen or lower alkyl,

including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

Accordingly, with respect to composition, there are provided compounds of formula I:



(I)

wherein:

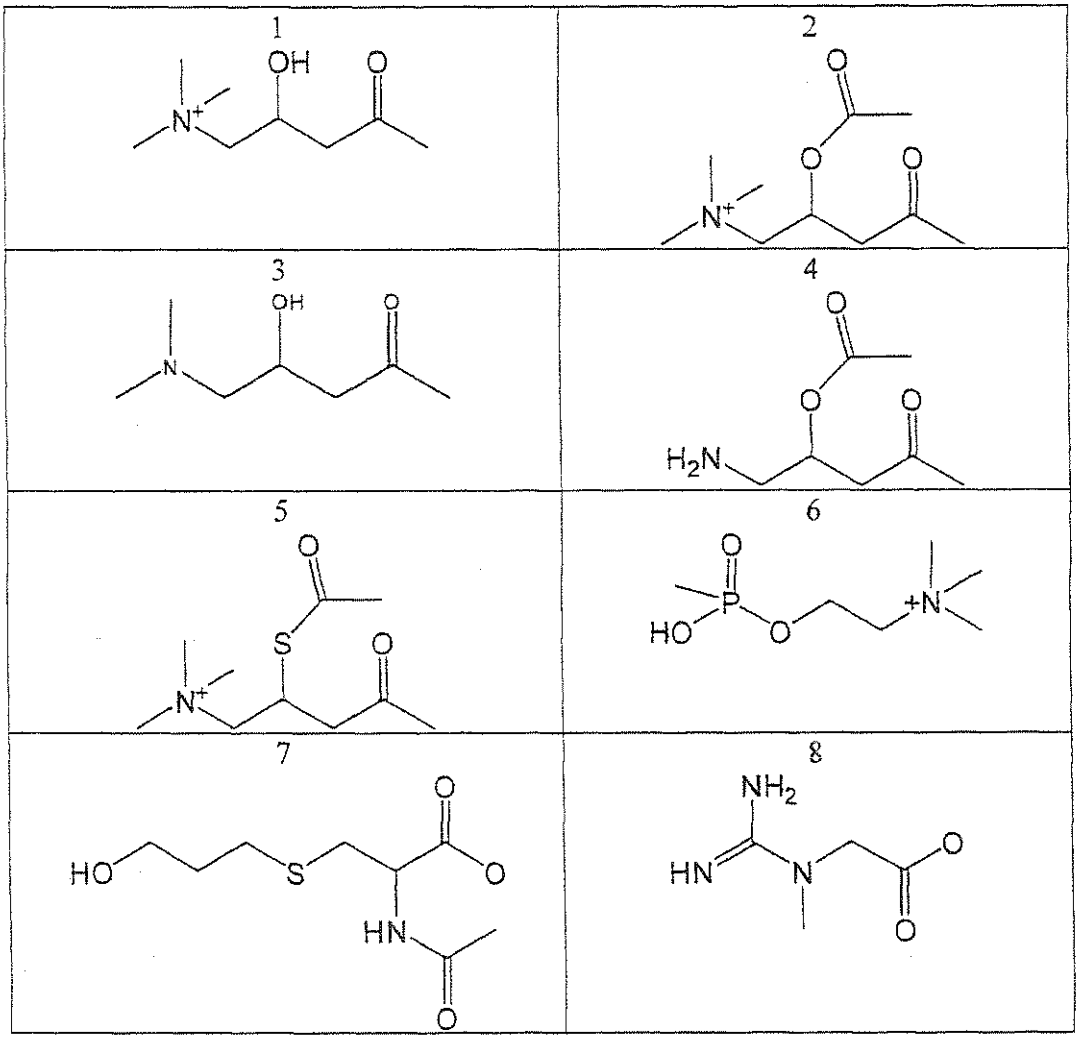
R_1 and R_2 can be the same or different; and are an alkyl or alkenyl hydrocarbon chain selected from Table 1 or 2;

Table 1: Alkyl and alkenyl hydrocarbon groups

No.	Chemical Structure	Abbr.
1	CH3(CH2)3-	C4:0
2	CH3(CH2)5-	C6:0
3	CH3(CH2)7-	C8:0

amino acids and groups of the structures shown below in Table 3.

Table 3



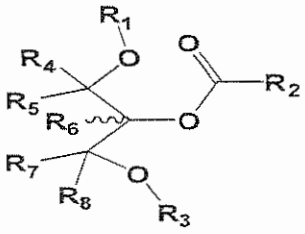
R_4 and R_5 are either the same or different and may be hydrogen or lower alkyl, for example methyl or ethyl;

R_6 is hydrogen or lower alkyl, for example methyl or ethyl; and

R_7 and R_8 are either the same or different and may be hydrogen or lower alkyl, for example methyl and ethyl,

and also including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

In yet another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula I:



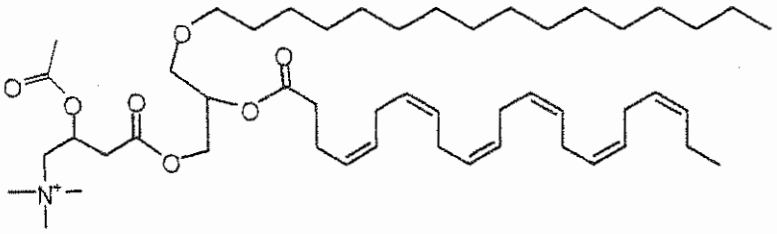
(I)

wherein R_1 to R_8 are as defined above, and including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

Another ~~aspect of this invention~~example is directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound as described above.

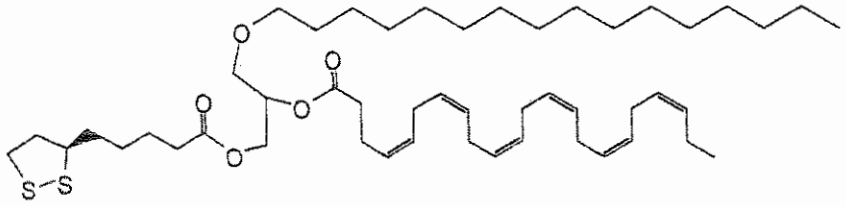
In one ~~embodiment~~example of the present ~~invention~~disclosure R_2 may be a docosahexaenoic acid (DHA) side chain, or $CH_3CH_2(CH{=}CHCH_2)_6CH_2$-.

In another ~~embodiment~~example, the compound can be 2-acetoxy-4-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4, 7,10, 13, 16, 19-hexaenoyloxy)-3-(hexadecyloxy)propoxy)-N,N,N-trimethyl-4-oxobutan-1-aminium.



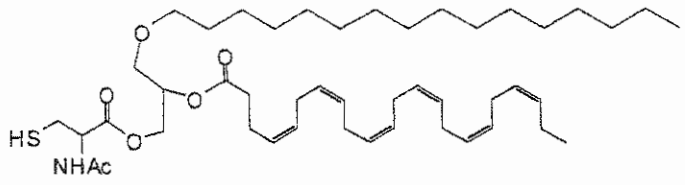
PPI-1009

In other ~~embodiments~~examples the compound may be (4Z, 7Z, 10Z, 13Z, 16Z, 19Z)-1-(5-((*R*)-1,2-dithiolan-3-yl)pentanoyloxy)-3-(hexadecyloxy)propan-2-yl docosa-4, 7, 10, 13, 16, 19-hexaenoate:



PPI-1011

or (4Z, 7Z, 10Z, 13Z, 16Z, 19Z)-1-(2-acetamido-3-mercaptopropanoyloxy)-3-(hexadecyloxy)propan-2-yl docosa-4, 7, 10, 13, 16, 19-hexaenoate:



PPI-1014.

The ~~invention~~present disclosure also includes pharmaceutical compositions comprising PPI-1009, PPI-1011, PPI-1014, or combinations thereof.

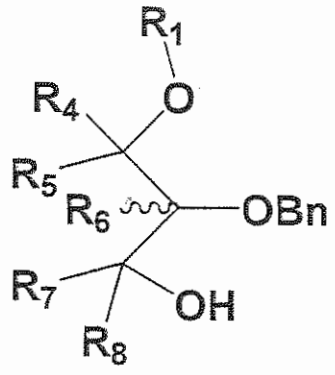
Without wishing to be bound by theory, certain ~~embodiments~~examples of the compounds described herein are believed to increase plasmalogen levels and the hydrolysis of acetyl-L-carnitine from sn-3 position, and may participate in potential molecular mechanisms that include: (i) acetylation of $-NH_2$ and –OH functional groups in amino acids and N-terminal amino acids in peptides and proteins resulting in modification of their structure, dynamic, function and turnover; and/or (ii) acting as a molecular chaperone to larger molecules resulting in a change in the structure, molecular dynamics, and function of the larger molecule.

Carnitine is important in the beta oxidation of fatty acids and the acetyl moiety can be used to maintain acetyl-CoA levels. Acetyl-L-carnitine (ALCAR) actions include modulation of: (i) brain energy and phospholipid metabolism; (iii) cellular macromolecules, including neurotrophic factors and hormones; (iii) synaptic morphology; and (iv) synaptic transmission of multiple neurotransmitters.

In one example~~According to a further aspect of the present invention~~ there is provided a method of treating or preventing diseases of aging mediated by plasmalogen deficiency, comprising administering to a patient in need thereof an effective amount of a compound or composition as described above.

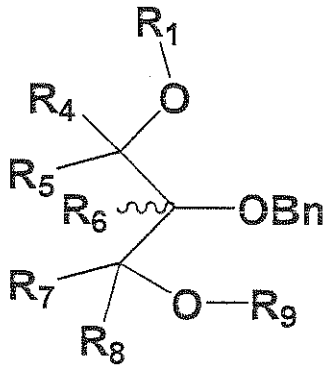
In another example~~a further aspect of the present invention~~ there is provided a method of treating diseases of aging associated with increased membrane cholesterol, increased amyloid and decreased plasmalogen levels comprising administering to a patient in need thereof, an effective amount of a compound or composition as described above.

In yet another aspect, there is provided a process for preparing a compound according to the structure of formula II:



(II)

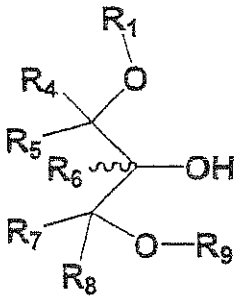
wherein R_1 and R_4 to R_8 are as defined above, and including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof, said process comprising reacting a compound of formula III:



(III)

wherein R_9 is a blocking group, in a suitable solvent with tetrabutylammonium fluoride (TBAF) under conditions to form said compound of formula II, and optionally purifying said compound of formula II.

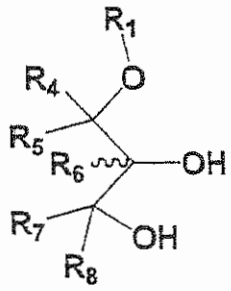
The ~~invention~~present disclosure also relates to a process for preparing a compound according to the structure of formula II:



(II)

wherein R_1 and R_4 to R_8 are as described above and R_9 is a blocking group, and including

racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof. The process involves reacting a compound of formula III:



(III)

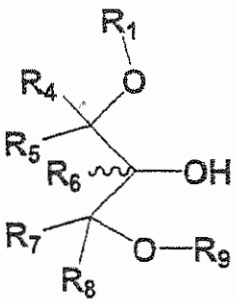
in a suitable solvent with a nucleophilic catalyst, a base and a blocking agent under conditions to form said compound of formula II, and optionally purifying the resulting compound.

In certain non-limiting ~~embodiments~~examples the blocking agent may be silane blocking agent, for instance a tert-butyldimethylsilyl halide which then gives rise to R_9 being a tert-butyldimethylsilyl group.

In other non-limiting ~~embodiments~~examples the nucleophilic catalyst may be DMAP, the base may be triethylamine, and the solvent may comprise dimethylformamide (DMF) and CH_2Cl_2.

Without wishing to be limiting, it may in certain ~~embodiments~~examples be preferred to prepare a solution including the compound of formula III, the nucleophilic catalyst, and the base in the appropriate solvent at from 0 to 5 °C prior to addition of the blocking agent, followed by addition of the blocking agent and then carrying out the reaction at a temperature of from about 15 to about 25 °C, for example at about 20 °C. The reaction will then preferably be allowed to proceed to completion, which may be up to 20 hours.

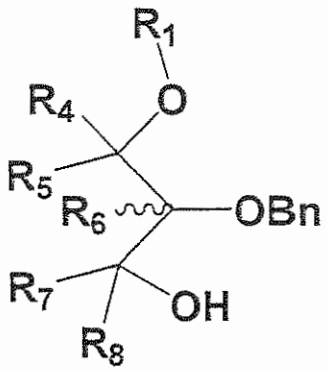
Also provided is an intermediate compound according to the structure of formula II:



(II)

wherein R_1 and R_4 to R_9 are as described above, including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

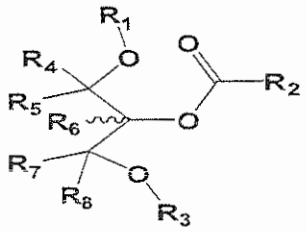
In yet another aspect, there is provided a compound according to the structure of formula II:



(II)

wherein R_1 and R_4 to R_8 are as defined above, including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

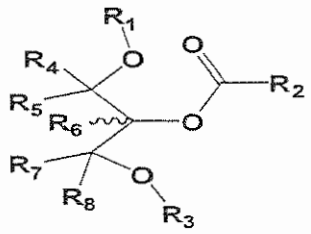
In yet another aspect, there is provided the use of a compound of formula I:



(I)

wherein R_1 to R_8 are as defined above, including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof, or a pharmaceutical composition comprising said compound admixed with a pharmaceutically acceptable carrier, for the manufacture of a medicament for treating or preventing diseases of aging associated with increased membrane cholesterol, increased amyloid or decreased plasmalogen levels, wherein the diseases of aging are selected from the group consisting of: neurodegeneration, cognitive impairment, dementia, cancer, and vascular disease.

In yet another aspect, there is provided the use of a compound of formula I:

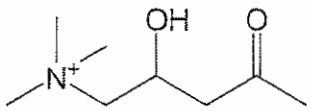


(I)

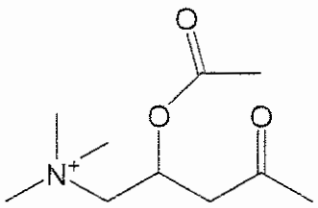
wherein

R_3 is selected from the group consisting of fatty acids having a chain of 4 to 28 carbons, carnitine, acetyl-D/L-carnitine, thiocarnitine, acetyl-D/L-thiocarnitine, creatine, norcarnitine, phosphocholine, lipoic acid, dihydrolipoic acid, phosphoethanolamine, phosphoserine, N-acetylcysteine, substituted or unsubstituted amino acid groups and groups of the structures shown below:

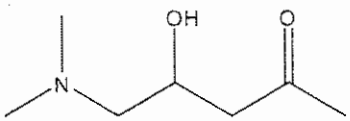
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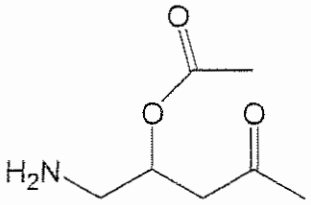
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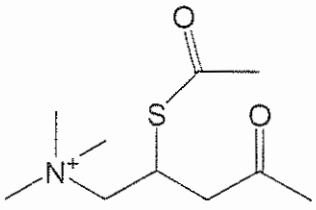
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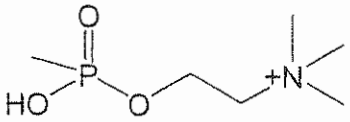
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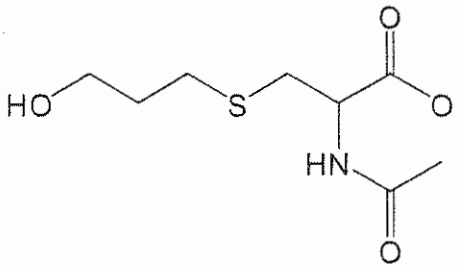
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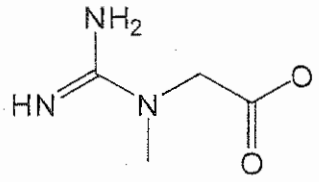
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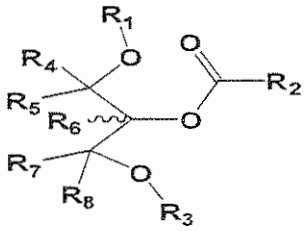


8



and R_1, R_2 and R_4 to R_8 are as defined above, including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof, or a pharmaceutical composition comprising said compound admixed with a pharmaceutically acceptable carrier, for the manufacture of a medicament for treating or preventing diseases of the aging mediated by plasmalogen deficiency, wherein the diseases of aging are selected from the group consisting of: neurodegeneration, cognitive impairment, dementia, cancer, and vascular disease, by increasing PlsEtn levels to above control levels in either PlsEtn deficient or PlsEtn sufficient systems.

In yet another aspect, there is provided the use of a compound of formula I:

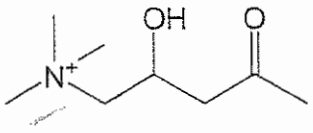


(I)

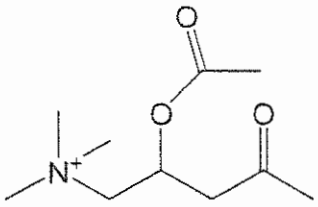
wherein

R_3 is selected from the group consisting of fatty acids having a chain of 4 to 28 carbons, carnitine, acetyl-D/L-carnitine, thiocarnitine, acetyl-D/L-thiocarnitine, creatine, norcarnitine, phosphocholine, lipoic acid, dihydrolipoic acid, phosphoethanolamine, phosphoserine, N-acetylcysteine, substituted or unsubstituted amino acid groups and groups of the structures shown below:

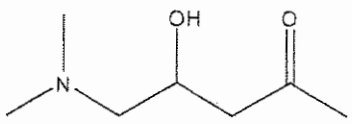
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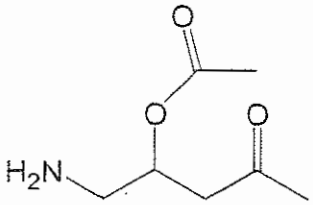
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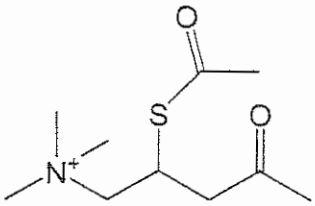
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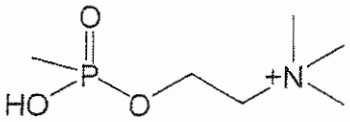
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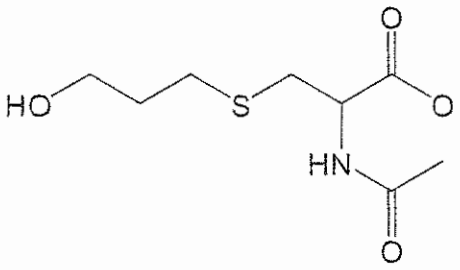
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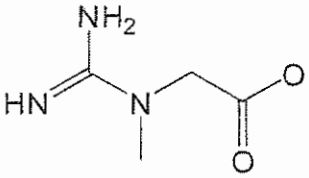
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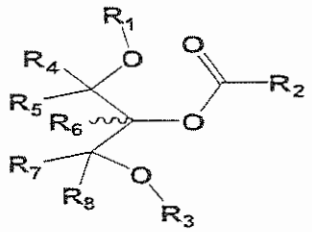


8



and R_1, R_2 and R_4 to R_8 are as defined above, including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof, or a pharmaceutical composition comprising said compound admixed with a pharmaceutically acceptable carrier, for the manufacture of a medicament for treating or preventing a disorder resulting from abnormal genetic expression of cholesterol transport proteins, wherein the disorder is selected from the group consisting of: neurodegeneration, cognitive impairment, dementia, cancer, and vascular disease.

In yet another aspect, there is provided the use of a compound of formula I:



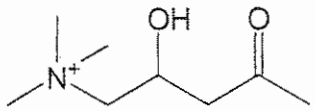
(I)

for the manufacture of a medicament for treating or preventing a neurodegeneration disease selected from the group consisting of Alzheimer's disease, Parkinson's disease and age-related macular degeneration, wherein

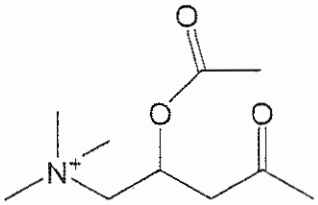
R_1 and R_2 are the same or different and selected from an alkyl or alkenyl hydrocarbon chain selected from the group consisting of: $CH_3(CH_2)_3$-, $CH_3(CH_2)_5$-, $CH_3(CH_2)_7$-, $CH_3(CH_2)_9$-, $CH_3(CH_2)_{11}$-, $CH_3(CH_2)_{13}$-, $CH_3(CH_2)_{15}$-, $CH_3(CH_2)_{17}$-, $CH_3(CH_2)_{19}$-, $CH_3(CH_2)_{21}$-, $CH_3(CH_2)_{23}$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7$-, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7$-, $CH_3CH_2(CH{=}CH)$-, $CH_3(CH_2)_3(CH{=}CH)$-, $CH_3(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_7(CH{=}CH)$-, $CH_3(CH_2)_9(CH{=}CH)$-, $CH_3(CH_2)_{11}(CH{=}CH)$-, $CH_3(CH_2)_{13}(CH{=}CH)$-, $CH_3(CH_2)_{15}(CH{=}CH)$-, $CH_3(CH_2)_{17}(CH{=}CH)$-, $CH_3(CH_2)_{19}(CH{=}CH)$-, $CH_3(CH_2)_{21}(CH{=}CH)$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_5(CH{=}CH)$, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6$-, $CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6$-, $CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2$-, $CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_{11}$, and $CH_3CH_2(CH{=}CHCH_2)_6CH_2$-;

R_3 is selected from the group consisting of fatty acids having a chain of 4 to 28 carbons, carnitine, acetyl-D/L-carnitine, thiocarnitine, acetyl-D/L-thiocarnitine, creatine, norcarnitine, phosphocholine, lipoic acid, dihydrolipoic acid, phosphoethanolamine, phosphoserine, N-acetylcysteine, substituted or unsubstituted amino acid groups and groups of the structures shown below:

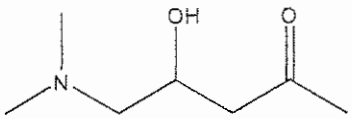
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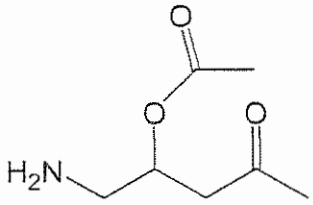
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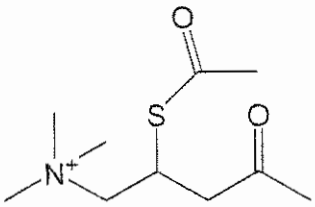
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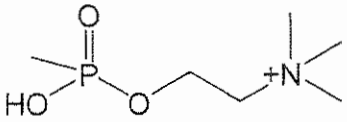
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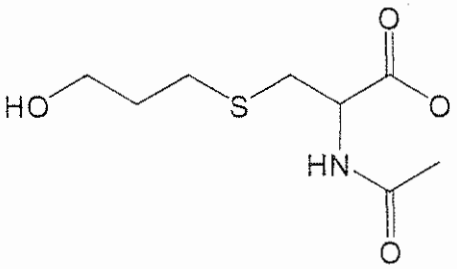
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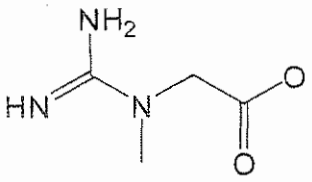
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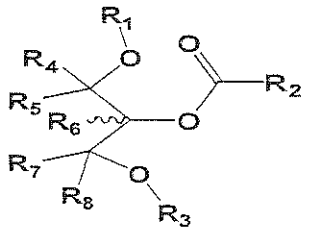
R_4 and R_5 are independently hydrogen or lower alkyl;

R_6 is hydrogen or lower alkyl; and

R_7 and R_8 are independently hydrogen or lower alkyl,

including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

In yet another aspect, there is provided the use of a compound of formula I:



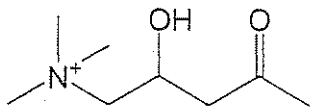
(I)

for the manufacture of a medicament for treating or preventing a vascular disease selected from the group consisting of atherosclerosis and hypercholesterolemia, wherein

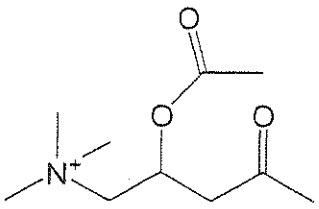
R_1 and R_2 are the same or different and selected from an alkyl or alkenyl hydrocarbon chain selected from the group consisting of: $CH_3(CH_2)_3$-, $CH_3(CH_2)_5$-, $CH_3(CH_2)_7$-, $CH_3(CH_2)_9$-, $CH_3(CH_2)_{11}$-, $CH_3(CH_2)_{13}$-, $CH_3(CH_2)_{15}$-, $CH_3(CH_2)_{17}$-, $CH_3(CH_2)_{19}$-, $CH_3(CH_2)_{21}$-, $CH_3(CH_2)_{23}$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7$-, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7$-, $CH_3CH_2(CH{=}CH)$-, $CH_3(CH_2)_3(CH{=}CH)$-, $CH_3(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_7(CH{=}CH)$-, $CH_3(CH_2)_9(CH{=}CH)$-, $CH_3(CH_2)_{11}(CH{=}CH)$-, $CH_3(CH_2)_{13}(CH{=}CH)$-, $CH_3(CH_2)_{15}(CH{=}CH)$-, $CH_3(CH_2)_{17}(CH{=}CH)$-, $CH_3(CH_2)_{19}(CH{=}CH)$-, $CH_3(CH_2)_{21}(CH{=}CH)$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_5(CH{=}CH)$, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_5(CH{=}CH)$-, $CH_3(CH_2)_3CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_5CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_7$-, $CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6$-, $CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6$-, $CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2$-, $CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2$-, $CH_3(CH_2)_7CH{=}CH(CH_2)_{11}$, and $CH_3CH_2(CH{=}CHCH_2)_6CH_2$-;

R_3 is selected from the group consisting of fatty acids having a chain of 4 to 28 carbons, carnitine, acetyl-D/L-carnitine, thiocarnitine, acetyl-D/L-thiocarnitine, creatine, norcarnitine, phosphocholine, lipoic acid, dihydrolipoic acid, phosphoethanolamine, phosphoserine, N-acetylcysteine, substituted or unsubstituted amino acid groups and groups of the structures shown below:

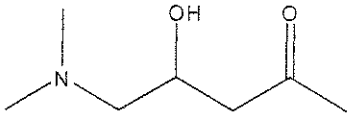
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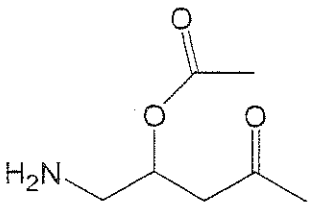
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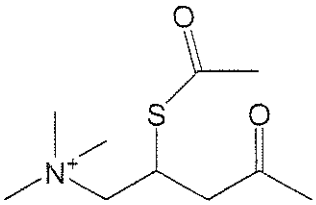
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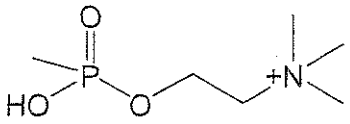
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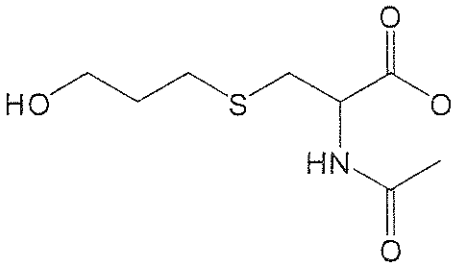
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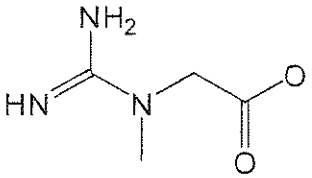
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R_4 and R_5 are independently hydrogen or lower alkyl;

R_6 is hydrogen or lower alkyl; and

R_7 and R_8 are independently hydrogen or lower alkyl,

including racemates or isolated stereoisomers and pharmaceutically acceptable salts or esters thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

FIGURE 1 shows the general experimental procedure for preparation of PPI-1009: 2-acetoxy-4-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4, 7,10, 13, 16, 19-hexaenoyloxy)-3-(hexadecyloxy)propoxy)-N,N,N-trimethyl-4-oxobutan-1-aminium, in accordance with an embodiment of the present invention.

FIGURE 2 shows decreased levels of total DHA plasmalogens in N-Rel cells, relative to control CHO cells, are restored in a concentration-dependent manner by PPI-1005 (R_1= 16:0; R_2=DHA; R_3=OH). 72 hr incubation. * p <0/05 vs. vehicle (veh).

FIGURE 3 shows (A) a time course of PPI-1009 (10 μM) incorporation into plasmalogens and lack of effect on cellular levels of chimyl alcohol or the associated alkenyl-acyl-glycerol (B) of N-Rel cells (0, 6, 12, 24, 48 and 72 hr). Cellular plasmalogens and docosahexaenoic (DHA) acid were quantitated by LC-MS/MS while chimyl alcohol was quantitated by GC-MS.

FIGURE 4 shows (A) the concentration-dependent (72 hr) increase of DHA plasmalogens in CHO cells with PPI-1005 and PPI-1009. While chimyl alcohol increased DHA-plasmalogens in N-Rel cells there was no effect in CHO cells (B). Cellular plasmalogens were quantitated by LC-MS and expressed relative to CHO controls or N-Rel controls.

FIGURE 5 shows the concentration response for the decrease in membrane cholesterol in N-Rel cells after a 48 hr incubation with 16:0(sn-1 alkyl)/DHA(sn-2 acyl) glycerol (PLM-05). Note that cholesterol levels are significantly elevated ($p < 0.05$) in NRel cells relative to CHO cells and that at 20 μM (PLM-05) decreases membrane free cholesterol and increases membrane cholesterol esters ($p < 0.05$).