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(54) **HIGH-EFFICIENCY FULLERENE-BASED RADICAL SCAVENGERS**

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(75) Inventors: **David F. Kronholm**, Brighton, MA (US); **Jan C. Hummelen**, Groningen (NL); **Alexander B. Sieval**, Groningen (NL)

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Correspondence Address:
WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109 (US)

(57) **ABSTRACT**

(73) Assignee: **Nano-C, Inc.**, Westwood, MA (US)

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Related U.S. Application Data

(60) Provisional application No. 60/529,988, filed on Dec. 15, 2003.

Chemically functionalized fullerenes are useful in various applications as radical scavengers. These chemically functionalized fullerenes offer the advantages of preservation of the high innate radical scavenging efficiency of the fullerene cage and ease of synthesis of fullerene derivatives of desirably altered chemical and physical properties and single isomers. Further, they are based on a common intermediate chemistry and intermediates can be easily functionalized and tailored to various requirements.

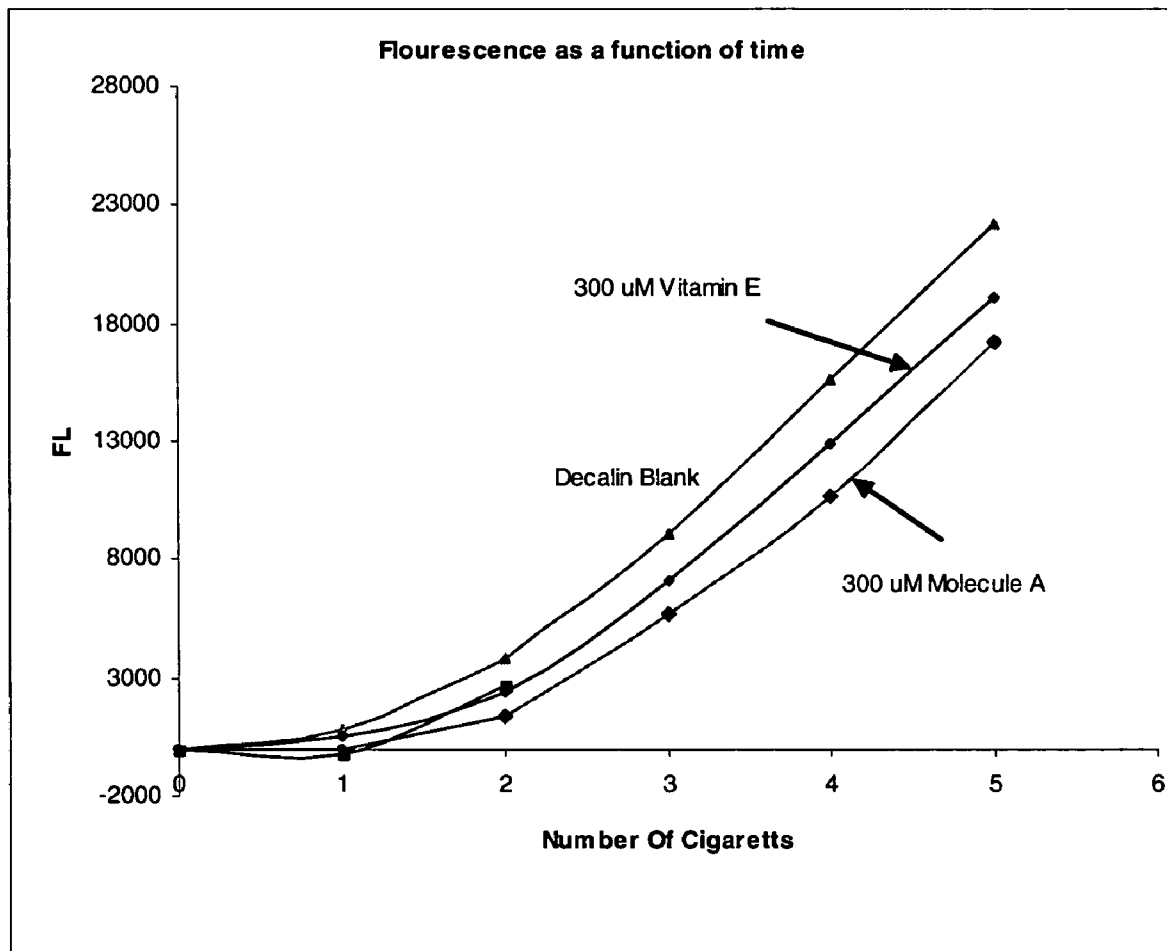


Figure 1

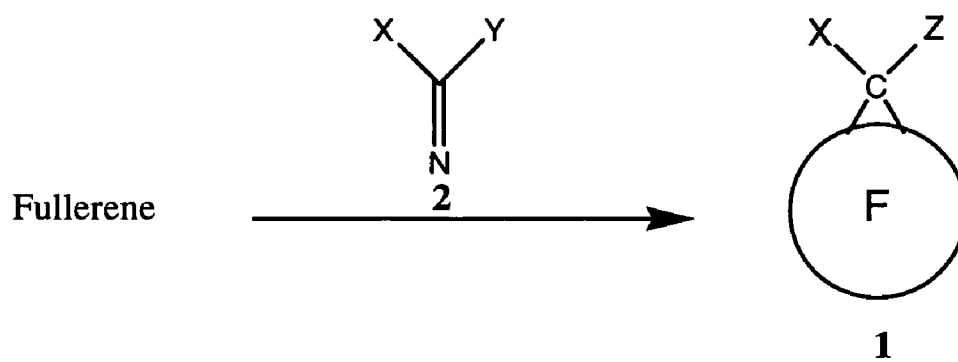
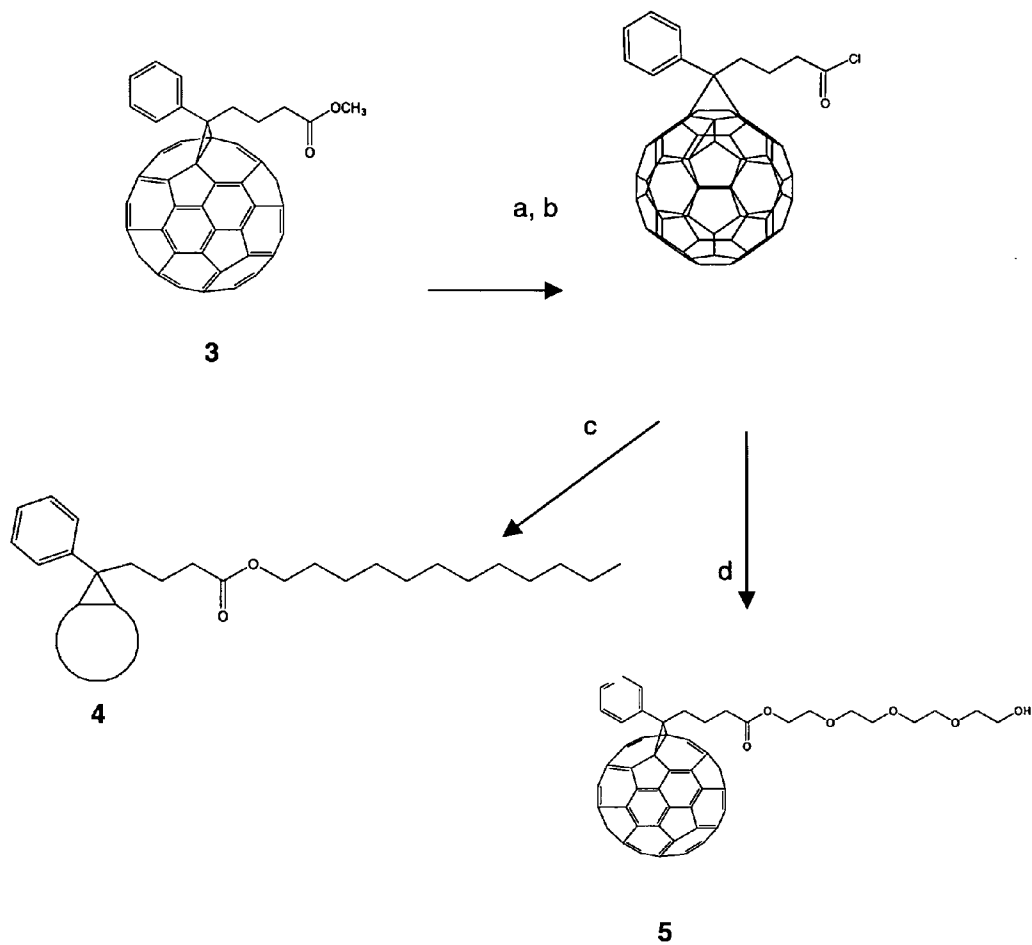
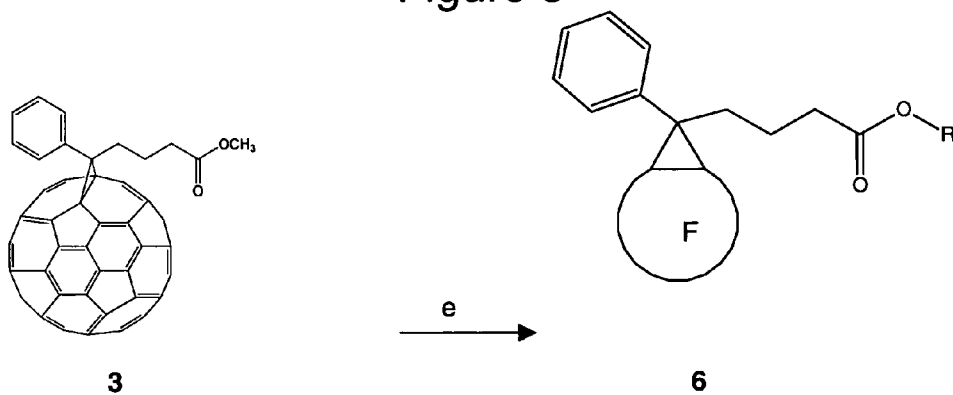


Figure 2

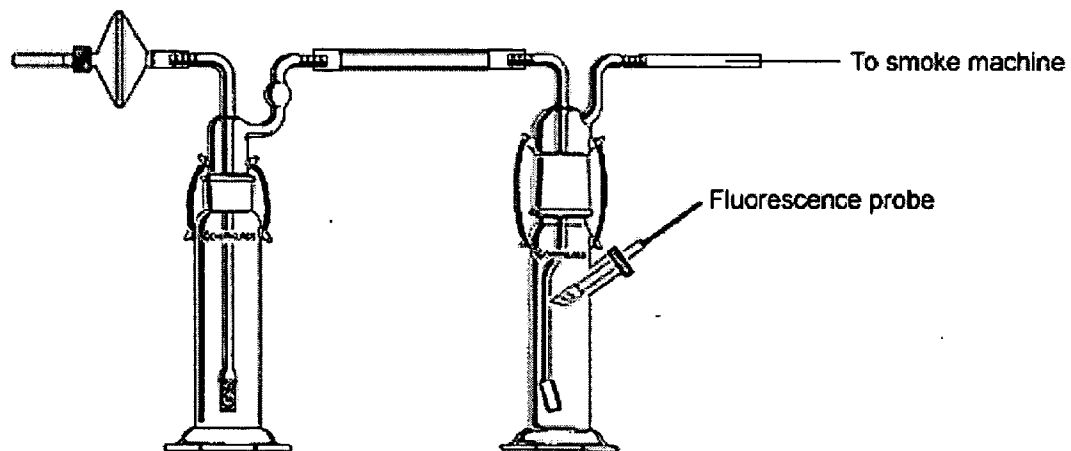


(a) aqueous HCl/AcOH/1,2-dichlorobenzene; (b) SOCl₂/CS₂; (c) ROH/pyridine, where R = C₁₂; (d) ROH/pyridine, where R = C₈H₁₇O₄

Figure 3



(e) R-OH/ Bu_2SnO /1,2-dichlorobenzene/heat; R = C_{12} ; $\text{C}_8\text{H}_{17}\text{O}_4$; or any group.



Experiment setup

Figure 5

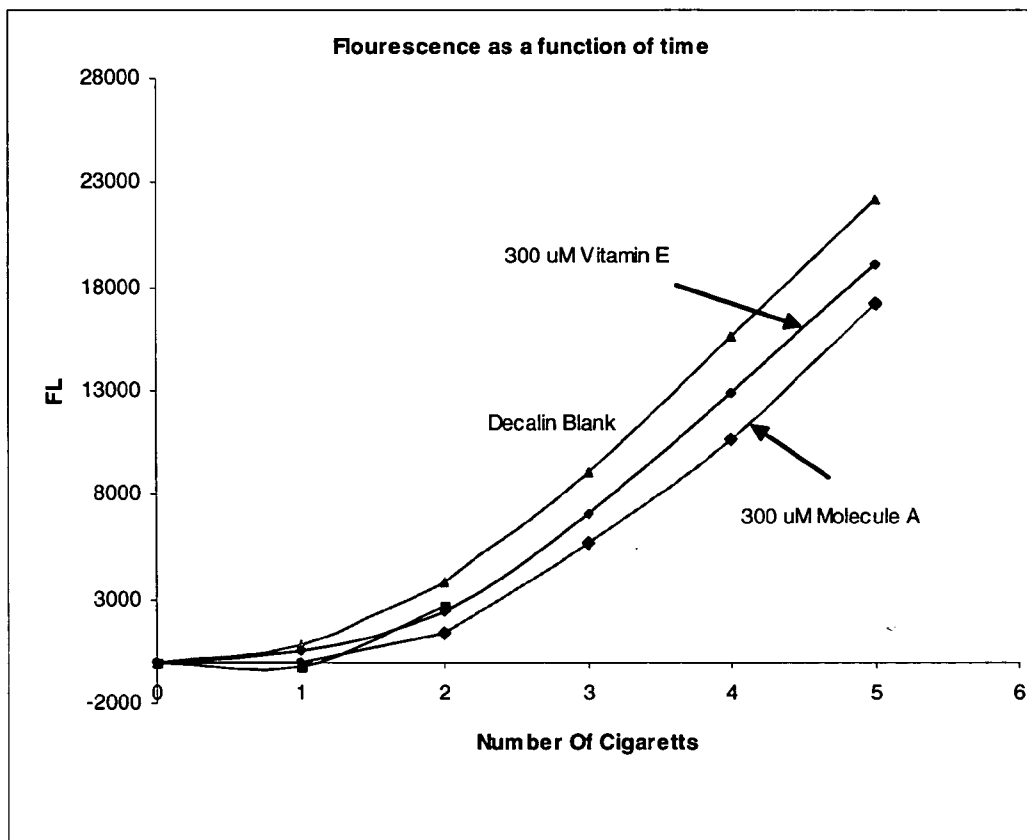


Figure 6A

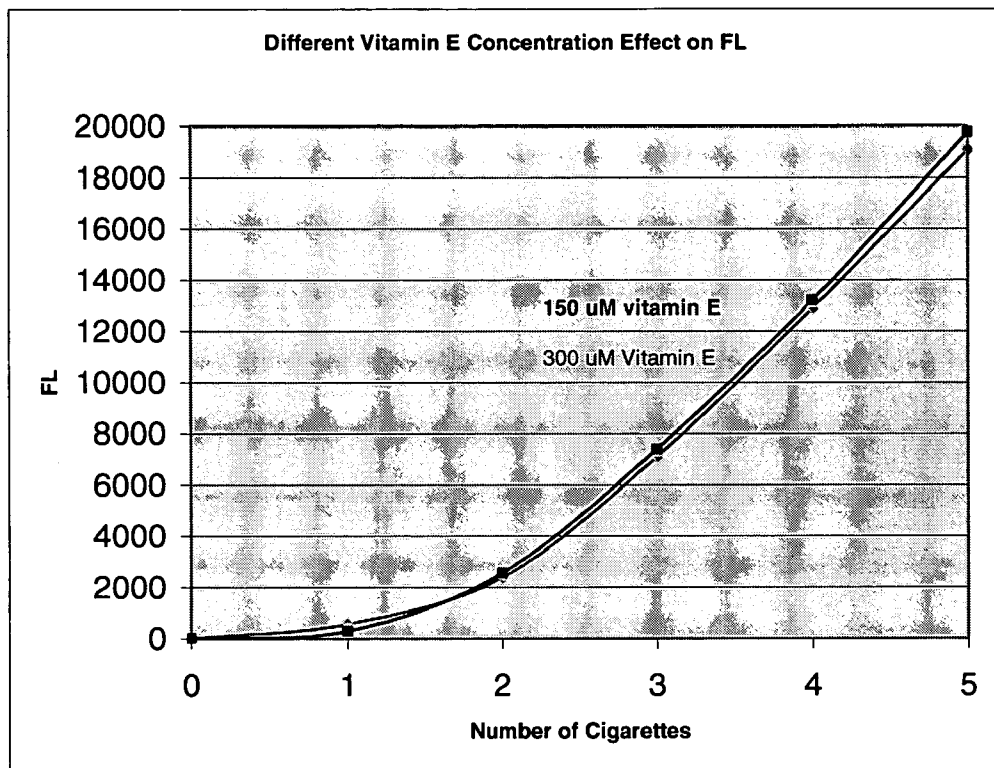


Figure 6B

HIGH-EFFICIENCY FULLERENE-BASED RADICAL SCAVENGERS

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to co-pending U.S. application Ser. No. 60/529988, filed on Dec. 15, 2003, entitled "Fullerene Derivatives Useful as Radical Scavengers/Antioxidants," the contents of which are incorporated in their entirety by reference.

[0002] This application is related to co-pending application entitled "Higher Fullerenes Useful as Radical Scavengers," and filed on even date herewith, the contents of which are incorporated in their entirety by reference.

FIELD OF THE INVENTION

[0003] This invention relates to fullerene derivatives useful as free radical scavengers.

BACKGROUND

[0004] Underivatized fullerenes and certain fullerene derivatives are known to be effective radical scavengers. Head to head comparisons of the reactivity towards radicals of C₆₀ and C₆₀ derivatives in solution have not been performed for radicals of practical interest, (e.g., reactive oxygen species or ROS), due to the differences in solubility. Fullerene derivatives made to date and tested as radical scavengers have been water soluble derivatives, whereas C₆₀ is water insoluble. Solvent, transport, and other effects thus do not allow direct comparison of the radical scavenging efficiency of these water soluble C₆₀ derivatives to C₆₀.

[0005] The native radical scavenging efficiency of C₆₀ is significantly altered depending on the properties and/or number of the addends on a derivatized fullerene. Typically, derivatized fullerenes exhibit reduced free radical scavenging efficiencies. Radical scavenging efficiency is reflected in the rate of reaction or the number of radicals scavenged per fullerene radical scavenger molecule. No clear relationship between the radical scavenging efficiency of a fullerene derivative and the type and number of addends has been established. It is also not well understood whether a drop in radical scavengers efficiency observed in derivatized fullerenes is due to a reduction in the rate of reaction or a reduction in the number of radicals scavenged per fullerene.

[0006] Chiang et al. (*Chem. Lett.*, 465-466 (1998)) report that at low concentrations, a water soluble polyhydroxylated fullerene derivative of average 18 addends has higher radical scavenging efficiency than a hexasulfobutylated fullerene having 6 addends. At higher concentrations, however, the hexasulfobutylated fullerene has a significantly higher radical scavenging efficiency. Chiang postulates that the higher radical scavenging efficiency of the hexasulfobutylated fullerene derivative at higher concentrations is due to smaller alteration of the electron affinity of the fullerene cage because of the smaller number of addends.

[0007] Thus radical scavenging efficiency may be affected by a variety of factors, including an alteration of the number of active sites due to the larger number of substitutions, a decrease in reactivity due to loss of strain in the fullerene cage, or an alteration of electron affinity of the fullerene reactive sites due to intra- and/or inter-molecular electronic interactions, or a combination of these effects. Differing

types and/or numbers of addends on the fullerene cage can give significantly different radical scavenging efficiencies due to alterations to the fullerene cage.

[0008] Conjugation of olefins with electron withdrawing groups (e.g. alcohols, carbonyls, etc.) in the vicinity of a radical scavenging carbon-carbon double bond may reduce the rate of radical addition (and resulting radical scavenging efficiency). This reduction is thought to occur by electron withdrawing inductive effects, which alter the electron density of the carbon-carbon double bond, and subsequently decreases the propensity of the carbon-carbon double bond to undergo radical addition reaction.

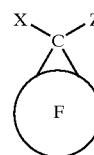
[0009] The difference in radical scavenging performance between different fullerene derivatives is not well understood. Under some conditions higher addend derivatives perform better than lower numbers of addends, and under other conditions, lower number addends perform better than higher number of addends. Similarly, under some conditions, electron-withdrawing groups perform better than non-electron-withdrawing groups. The nature of the interaction of the fullerene cage and the addends to the cage is not presently well enough understood in the art to provide a clear prediction on the relative performance of different fullerene derivatives relative to the performance of the fullerene cage.

SUMMARY

[0010] In one aspect of the invention, a class of compounds is identified having surprisingly high radical scavenging efficiencies. The compounds preserve the inherent physical and chemical nature of the fullerene cage so as to preserve the high radical scavenging efficiency of the fullerene molecule, while providing derivatization flexibility. Such flexibility provides control over solubility, transport, and other properties in use conditions.

[0011] In another aspect of the invention, a method is provided for the scavenging (or reduction) of free radicals from a target. The target is exposed to a class of fullerene derivatives to reduce the level of free radicals in the target. The class of compounds useful as free radical scavengers may be functionalized with chemical moieties so that the chemical and/or physical properties of the substituent fullerene may be altered without significant alteration of the inherent physical and chemical nature of the fullerene cage so as to preserve the radical scavenging efficiency of the fullerene cage.

[0012] In one aspect of the invention, a method of scavenging free radicals in or on a target includes exposing a target to a compound having the formula:



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[0013] where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms, where X is

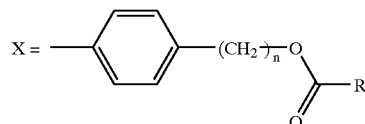
$(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitrites, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

[0014] In one or more embodiments, C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group.

[0015] In one or more embodiments, C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is an alkyl carbon and R'' is independently selected from the group consisting of alkyl and alkyl moieties bearing any hetero or functional group.

[0016] In one or more embodiments, wherein Z is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons, or at least 12 carbons, or at least 16 carbons.

[0017] In one or more embodiments, the compound has the formula $(F)(C)(X)(Z)$, wherein



where F is a fullerene ring, and where n is in the range of 1 to 20, and R is any chemical group.

[0018] In one or more embodiments, the compound includes two to four $C(X)(Z)$ adducts on the fullerene ring.

[0019] In one or more embodiments, the fullerene contains from about 60 to about 120 carbon atoms. The fullerene compound can be a [5,6] fulleroid or a [6,6] methanofullerene. X and Z are different.

[0020] In one or more embodiments, X and/or Z is a lipophilic moiety, and the lipophilic moiety is selected from the group consisting of fatty acids, fatty amides, fatty alcohols, and fatty amines, and the compound is capable of transport through lipid phases in a biological system.

[0021] In one or more embodiments, X and/or Z is a hydrophilic moiety, and the compound is capable of transport through aqueous phases in a biological system.

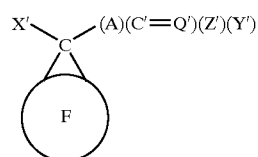
[0022] In one or more embodiments, X and/or Z is a chemical moiety that is independently effective as a free radical scavenger.

[0023] In one or more embodiments, X and/or Z is an amphiphilic moiety.

[0024] In one or more embodiments, X is a lipophilic and Z is a hydrophilic moiety, or vice versa.

[0025] In one or more embodiments, X is a lipophilic and Z is a hydrophilic moiety, or vice versa, such that the fullerene compound is amphiphilic.

[0026] In one aspect of the invention, a method of scavenging free radicals from in or on a target includes reacting a radical species present in a biological system with a compound having the formula:



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[0027] where the ring, F , comprises a fullerene comprising from about 20 to about 240 carbon atoms, where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl; A is an aliphatic group containing 1 to 20 carbon atoms, or 3 to 12 carbon atoms; Q' is O, N or S and if Q' is N, N can be bound to any group; Z' is bound to C' and is halogen, O, N, or S, and Y' is bound to Z' and is any chemical group or any salts thereof.

[0028] In one or more embodiments, Z' and Q' are O.

[0029] In one or more embodiments, $Y'40$ is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons or at least 8 carbons, or at least 12 carbons, or at least 18 carbons.

[0030] In one or more embodiments, Y' is a chemical moiety that is independently effective as a free radical scavenger, Y' is an amphiphilic moiety, or Y' is selected from the group consisting of sugars, histamines, amino acids and carotenoids.

[0031] In one or more embodiments, $-(C'(=Q')(Z')(Y'))$ in combination includes a carboxylic acid (or carboxylate), ester, amide, anhydride, acid halide, lactone, or lactam species.

[0032] In one or more embodiments, the compound includes [6,6]-phenyl C_{61} -butyric acid methyl ester (PCBM), where X' is phenyl, A is $(CH_2)_3$, Q' is O, Z' is O, and Y' is CH_3 .

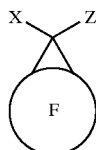
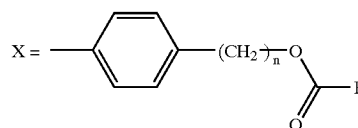
[0033] In one or more embodiments, the compound includes two or more adducts of $C(X')((A)(C'(=Q')(Z')(Y'))$ with the fullerene ring.

[0034] In one or more embodiments, a method of scavenging a free radical further includes exposing the target to at least one additional radical scavenging compound.

[0035] In one or more embodiments, a method of scavenging a free radical further includes including an additive selected to enhance or preserve the efficacy of the compound.

[0036] In one aspect, method for preventing or reducing lipid peroxidation in a biological system, reducing oxidative stress in a biological system, or altering radical mediated chemical pathways in a biological system are provided.

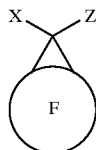
[0037] In one aspect of the invention, a compound is provided having the formula:



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[0038] wherein the ring F carbon atoms X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties and Z contains a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons, or 8 carbons, or 12 carbons, or 16 carbons, or 18 carbons.

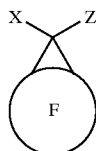
[0039] In one aspect of the invention, a compound is provided having the formula:



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[0040] wherein where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms, where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and wherein Z contains $O(CH_2CH_2O)_mCH_2CH_2OP$, where P is H or alkyl or aryl, and m is in the range of 1 to 100. In one or more embodiments, X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties

[0041] In one aspect of the invention, a compound has the formula:

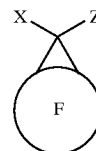


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[0042] wherein where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms, X has the formula:

[0043] where R is any chemical group, and n is in the range of 1 to 20; and where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitrites, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like. In one or more embodiments, R is alkyl or R is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons, or at least 8 carbons, or at least 12 carbons, or at least 16 carbons.

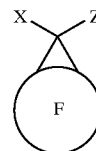
[0044] In one aspect of the invention, a composition has the formula:



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[0045] where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and Z contains a radical scavenging moiety selected from the group consisting of carotenoids, flavonoids, anthocyanidins, lipoic acids, ubiquinoids, and retinoids. In one or more embodiments, X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties.

[0046] In another aspect of the invention, a composition has the formula:



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[0047] where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and wherein Z contains $O(CH_2CH_2CH_2O)_mCH_2CH_2CH_2OP$, where P is H or alkyl or aryl, and m is in the range of 1 to

100. In one or more embodiments, X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties.

BRIEF DESCRIPTION OF THE DRAWING

[0048] Various embodiments of the invention are described with reference to the drawing, which is provided for the purpose of illustration only and is not intended to be limiting of the invention, the full scope of which is set forth in the claims below.

[0049] FIG. 1 is a general scheme for the preparation of a substituted methanofullerene by reaction with a diazo compound.

[0050] FIG. 2 illustrates a reaction scheme for the derivatization of a methanofullerene by acyl halide displacement.

[0051] FIG. 3 illustrates a reaction scheme for the derivatization of a methanofullerene by transesterification from a PCBM molecule.

[0052] FIGS. 4A and 4B illustrate reaction schemes for the direct formation of a derivatized methanofullerene according to one or more embodiments of the present invention.

[0053] FIG. 5 is a schematic illustration of the apparatus used to determine free radical scavenging.

[0054] FIGS. 6A and 6B are plots of fluorescence resulting from the reaction of radicals contained in cigarette smoke with a dye which fluoresces upon reaction with radicals in the presence of various free radical scavenging molecules.

DETAILED DESCRIPTION

[0055] For application of fullerenes as radical scavengers in various settings, it is useful to form fullerene derivatives which preserve to the highest extent possible the high efficiency of the radical scavenging properties of the fullerene cage without detrimentally altering the electron affinity, energetic strain, number of reactive sites, steric availability, etc. of the fullerene cage. Further, it is useful to form fullerene derivative intermediates to allow for formation of a variety of new fullerene derivatives with various functionalities, e.g., lipophilic, hydrophilic or amphiphilic fullerenes, that do not significantly differ in radical scavenging efficiency from their fullerene parent.

[0056] Various methanofullerenes are disclosed having one or more non-electron withdrawing groups as substituents to the methanocarbon. The absence or reduction of electron withdrawal on the fullerene cage helps to maintain the free radical scavenging capability of the fullerene molecule. The chemical and/or physical functionality of the fullerene is adjusted by modification of the methanocarbon adduct instead of the fullerene cage. Modifications are provided to obtain enhanced lipophilicity, hydrophilicity, amphiphilicity or other properties of the methanofullerene.

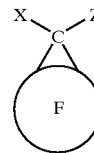
[0057] By "adduct" as the term is used with reference to methanofullerenes, it is meant the addition of a methylene group to the fullerene cage resulting in the formation of a cyclopropane ring. The carbon atom in the cyclopropanyl adduct is termed the methanocarbon. Functional groups may be attached to the available sites on the methanocarbon.

[0058] The term "fullerene" is used herein to refer to any closed cage carbon compound containing both five- and six-membered carbon rings independent of size and is intended to include, without limitation, the fullerenes C₆₀, C₇₀, C₇₂, C₇₆, C₇₈, C₈₂, C₈₄, C₈₆, C₉₀, C₉₂, and C₉₄.

[0059] Electron withdrawing groups are groups that are more electronegative than the methanocarbon atom such as groups that contain O, N, P, or S. In close proximity to the methanocarbon, they may have electron withdrawing inductive effects on the fullerene cage. Electron withdrawing groups that are one carbon removed from the methanocarbon may also contribute inductive effects to the fullerene carbon atoms, and it is possible that some functional groups at larger distances from the fullerene may show electron withdrawing effects through space. Electron withdrawing groups include groups having a carbon atom directly bonded to the methanocarbon (an "alpha-carbon"), which form a double or triple bond with the alpha-carbon. Electron withdrawing groups include groups which contain O, N, P, or S atoms, such as COOH, COOR, C(O)SR, CON(H)R, C(O)N(R₁)(R₂), CHO, COR, CSR, CN, P(O)(OR), SO₂R, NO₂, and the like.

[0060] Exemplary non-electron withdrawing groups are obtained by including an alpha-carbon lacking a double or triple bond to an electronegative atom such as O, N or S in one or more of the functional groups pendant to the methanocarbon. Aromatic, alkyl, alkenyl, and alkynyl alpha-carbons are linked to an additional chemical moiety or H. By directly linking electron donating or electron neutral moieties at the methanocarbon, the electronic and chemical integrity of the fullerene cage is better preserved. Electron withdrawing groups or other moieties may be tethered to the fullerene at a distance from the fullerene, without these groups being in close proximity to the fullerene cage, so as to preserve the inherent radical scavenging efficiency of the fullerene. Such electron withdrawing functional groups may be desirable to accomplish other objectives of the molecule, such as, attaining desired solubility, transport or binding characteristics.

[0061] A free radical may be scavenged from on or in a target by exposing the target to a compound having the formula,



[0062] where the ring, F, is a fullerene comprising from about 20 to about 240 carbon atoms, or about 60 to about 120 carbon atoms; where X is (C')(R')_n and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and where Z is (C'')(R'')_n and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is selected such that Z is a non-electron withdrawing group, and n=1, 2, or 3, or Z is an electron-

withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitrites, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

[0063] In one or more embodiments, C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is (C'')(R'')_n and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is selected such that Z is a non-electron withdrawing group.

[0064] In one or more embodiments, C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is (C'')(R'')_n and C'' is an alkyl carbon and R'' is selected from the group consisting of alkyl and alkyl moieties bearing any hetero or functional group.

[0065] The groups (C')(R')_n and (C'')(R'')_n define non-electron withdrawing functional moieties. By way of example, the groups may include alkyls, cyclic alkyls, and substituted alkyls, alkylaryls, alkyl ethers, alkylaryl ethers, alkyl thioethers, alkylaryl thioethers, alkyl esters, alkylaryl esters, alkyl thioesters, alkylaryl thioesters, alkyl amides, alkylaryl amides, alkyl amines, alkylaryl amines, alkyl anhydrides, alkylaryl anhydrides, alkyl carbonates (or carboxylic acids) and alkylaryl carbonates. By way of example, the groups may include substituted aryls such as arylalkyls, aryl ethers, arylalkyl ethers, aryl thioethers, arylalkyl thioethers, aryl esters, arylalkyl esters, aryl thioesters, arylalkyl thioesters, aryl amides, arylalkyl amides, aryl amines, arylalkyl amines, aryl anhydrides, arylalkyl anhydrides, aryl carbonates (or carboxylic acids) and arylalkyl carbonates. Other substitutes are contemplated within the scope of the invention.

[0066] In one or more embodiments, X and/or Y of compound 1 include chemical moieties that provide lipophilic (or hydrophobic) functionality, i.e., having an affinity for lipid-like materials. Lipids include fatlike substances characterized by being water insoluble and being extractable by nonpolar (or organic) solvents such as alcohol, ether, chloroform, benzene, etc. All contain as a major constituent aliphatic hydrocarbons. Suitable lipophilic moieties for use in free radical scavenging include long-chain alkanes or substituted long-chain alkanes (6 or more carbon atoms, preferably 12 or more carbon atoms), which may be branched, and which may contain various other chemical groups have affinity with lipids. Compounds containing lipophilic moieties are useful in the transport of the free radical scavenging compound through lipid phases in a biological system or hydrophobic phases in a chemical system.

[0067] Exemplary lipophilic groups include fatty alcohol and fatty acid ester, fatty amide, fatty amine moieties, such as isostearic acid derivatives, or functional groups derived from molecules such as isopropyl palmitate, isopropyl isostearate, stearyl stearate, diisopropyl adipate, octyl palmitate, isopropyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, glyceryl oleate, methyl oleate, isobutyl oleate, tocopheryl linoleate, arachidyl propionate, myristyl lactate, decyl oleate, isopropyl lanolate, neopentylglycol dicaprylate/dica-

prate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, octyl dodecanol, sucrose esters of fatty acids, octyl hydroxystearate, stearamide, oleamide, and erucamide.

[0068] In one or more embodiments, X and/or Y of compound 1 include chemical moieties that provide hydrophilic functionality, i.e., having an affinity to water or hydrophilic materials. Groups which may provide hydrophilic functionality include poly-(ethylene oxide)s, mono-, di- or poly-hydroxylated alkanes, mono-, di- or poly-hydroxylated cycloalkanes, amino alkanes, diamino alkanes, mono-, di-, or poly-saccharides, ammonium groups, alkylated ammonium groups, phosphates, alkylphosphates, sulfonates, and alkylsulfonates. Compounds containing hydrophilic moieties are useful in the transport of the free radical scavenging compound through aqueous phases in a biological or chemical system.

[0069] In one or more embodiments, X and/or Y of compound 1 include chemical moieties that provide amphiphilic functionality. Amphiphilic functionality refers to molecules that have both lipophilicity and hydrophilicity. Groups which provide amphiphilic functionality include polyethylene glycol, poly(ethylene oxide)s, propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, and other glycols. Alternatively, amphiphilic properties may be obtained by selecting lipophilic and hydrophilic properties for the X- and Y-substituents of compound 1, respectively, or vice versa.

[0070] In still other embodiments, X and/or Y of compound 1 include chemical moieties that provide biofunctionality. Thus X and/or Y may be a sugar, histamine, amino acid or carotenoid and the like. The X and/or Y groups of compound 1 may also include a chemical moiety that is independently effective as a free radical, for example, flavenoids, carotenoids, anthocyanidins, lipoic acids, ubiquinoids, retinoids or Vitamin E moieties.

[0071] Methanofullerenes having a minimal number of adducts, e.g., a monoadduct or 2-3 adducts, allows the alteration of the chemical and physical properties of the fullerene in a desirable way, while preserving to a great degree the strain and number of olefin bonds, steric availability, and other properties of the fullerene cage. The absence or reduction of electron-withdrawing groups adjacent to the fullerene cage also maintains or enhances free radical scavenging efficiencies.

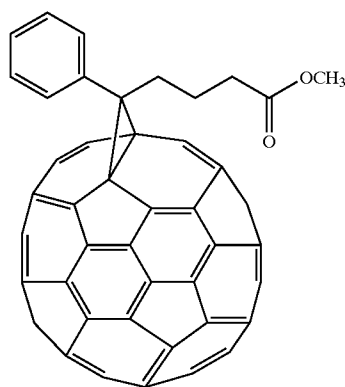
[0072] Steric hindrance is also minimized through a small number of addends to the fullerene cage. At the same time, the molecules described here conveniently allow for various modifications to the chemical and physical functionality of the fullerene molecule, while maintaining a constant configuration adjacent to the fullerene cage (the methano bridge), allowing for the reliable synthesis of new high efficiency fullerene-based radical scavengers for application in a variety of settings.

[0073] In particular, monoadducts provide for the least disruption of the chemical and physical nature of the fullerene cage, and allow for convenient synthesis of single isomers. However, di, tri and higher adducts may be used in the radical scavenging processes described herein.

[0074] Further still, it is useful to have a common addition chemistry through which chemical moieties having various functionalities may be added to a fullerene.

[0075] Various methanofullerenes are known in the art, and synthesis of these compounds through diazoalkane addition chemistry has the advantage of being simple synthetic chemistry and providing monoadducts in high yield. This reaction is illustrated schematically in FIG. 1. A fullerene compound is reacted with a diazo compound 2 to provide a functionalized methanofullerene 1. Diazoalkane addition results first in [6,6] diazoline adducts that can expel N_2 and yield [5,6] fulleroids, which can be isomerized to [6,6].methano-bridged fullerenes. The diazoalkane precursors are typically formed in situ. By way of example, X and Z of the diazo compound 2 can be moieties as described herein for the methanofullerene compound or they may be intermediates containing reactive groups capable of further reaction to form the desired X, Z functional groups of the methanocarbon. Further, similar diazoalkane addition chemistry may be used to form multiple methanocarbon adducts on the fullerene cage, fullerene derivatives using either the same or different diazoalkane precursors. This provides a synthetic route to variously substituted methanofullerene compounds that may be used in the free radical scavenging processes described herein.

[0076] The fullerene derivative [6,6]-phenyl C_{61} -butyric acid methyl ester (PCBM) 3 is an example of a fullerene derivative formed through diazoalkane addition chemistry, where the diazoalkane is a 1-phenyl-1-(3-(methoxycarbonyl)propyl)diazomethane. The synthesis by diazoalkane addition of cyclopropanyl-based fullerene derivatives (methanofullerenes) such as PCBM 3 may be accomplished by combining, with stirring, the diazocompound and fullerene C_{60} .



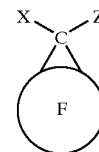
[0077] The ester functional group (e.g., methyl ester in compound 3) allows for convenient synthesis of a large number of compounds, through displacement pathways illustrated in the reaction scheme of FIG. 2, or transesterifications illustrated FIG. 3. PCBM 3 can be used as a chemical intermediate to synthesize an unlimited number of new fullerene derivatives having various functionalities. The compound 3 is first converted using reaction steps (a) [aqueous HCUACoH/1,2-dichlorobenzene (ODCB)] and (b) [SOCl₂/CS₂] into the corresponding acid chloride 3a. The acid chloride 3a is then displaced by various groups to form a wide range of functionalized ester derivatives. Examples of this can be found in the literature (for example, see Hummelen et al., *J. Org. Chem.* 1995, 60, 532). Thus, in

FIG. 2, the methyl group is displaced to form a C12 alkyl ester 4 using reaction steps (c) [ROH/pyridine; R=C12] or a polyethylene glycol ester 5 using reaction step (d) [ROH/pyridine; R=C₈H₁₇O₄]. Alternatively, PCBM 3 is transesterified using reaction step (e) [ROH/Bu₂SuO/1,2-dichlorobenzene/heat] to obtain a transesterification compound 6. The synthesis of several compounds, including compounds 4 and 5, by this method is described below.

[0078] A preferred method for transesterification of any fullerene compound having carboxylic esters anywhere or in any number is the use of dibutyltin oxide as catalyst for the reaction. This reaction gives high conversions from one ester group into another ester group and can also be used for mild deprotection conditions (e.g., when removing an acetate group in the presence of another ester moiety). The advantage of direct transesterification over the route using acid halides as shown for compound 3a is the reduction of the number of reactions that is required to prepare the desired carboxylic ester group. Other transesterification techniques that have been tried with fullerene esters such as acid catalysis do not give satisfactory conversions. Anionic transesterifications also are not satisfactory with fullerene esters because fullerenes react with the anion and give side products. Dibutyltin oxide surprisingly gives very satisfactory yields under mild conditions for transesterification of fullerenes.

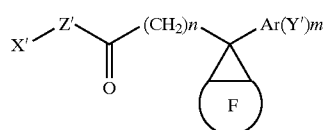
[0079] Alternatively, diazoalkane addition chemistry can be used by forming the desired functionalized diazo compound before reaction with the fullerene molecule. See FIGS. 4A and 4B, where the appropriate diazo compound is selected to provide alkyl ester functionalized methanofullerenes 7 and aryl functionalized methanofullerenes containing ester groups bound to a substituent of the aryl group 8. The ester group may also be bound directly to the aryl group.

[0080] The above methods allow for forming part (for example as shown in FIGS. 2 and 3) or all (for example as shown in FIGS. 4A and 4B) of the adduct added to the fullerene molecule of the following general form 1 all through diazoalkane addition chemistry,



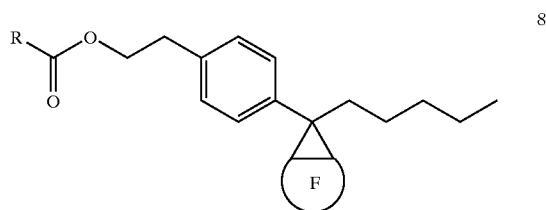
[0081] where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms, where X is (C')(R')_n and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and where Z is (C'')(R'')_n and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is selected such that Z is a non-electron withdrawing group, and n=1, 2, or 3, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitriles, amides, thioaldehydes, thioketones, thioesters, amide esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

[0082] A specific embodiment of compound 1 is shown below (compound 7), where Y' is any substituent on the aryl group; Ar is any aryl group; m greater than or equal to zero and indicates the total number of independent substituents Y' on the aryl group; n=1 to 20; Z' is any heteroatom (e.g., O, N, S); X' is any chemical group; and F is a closed cage all-carbon molecule (fullerene) with 20 to 240 carbon atoms (preferably 60 to 120).



[0083] Methanofullerenes containing an aryl functional group at the X-position in compound 1 may be conveniently synthesized from the precursor diazoalkane because common aromatic chemistry, such as Friedel Crafts acylation, can be used to prepare the diazo precursor. Also, it has been observed that aryl-substituted methanofullerenes are more amenable to photoisomerization from [5,6] fulleroids to [6,6] methano bridges.

[0084] Another specific embodiment of compound 1 is shown below (compound 8). Longer and shorter alkyl chains are contemplated and the alkyl chain may contain between about 2 to 20 carbon atoms. In addition, R may be aryl or a long chain, branched or linear, saturated or unsaturated carbon chain having 1-20 carbons.



[0085] The fullerene molecules used in the present invention, may be any fullerene, preferably fullerenes commonly synthesized such as C₆₀, C₇₀, C₇₂, C₇₆, C₇₈, C₈₂, C₈₄, C₈₆, C₉₀, C₉₂, and C₉₄. Different fullerenes may be more desirable than others for different applications.

[0086] The molecules described above are useful for scavenging any type of radical, such as, but not limited to, radicals of biological importance, such as reactive oxygen species: —OH, —O₂—, ROO—; NO_x radicals; products of biological radical pathways such as fatty acid radicals and the products of biological radical scavengers reacting with radicals, such as tocopherol, ubiquinol, and ascorbyl radicals; auto-oxidation and products of auto-oxidation in polymer and other systems, such as food; radicals of environmental sources such as cigarette smoke and environmental combustion sources, such as automobile exhaust. Also, the present molecules may be used to scavenge radicals in radical polymerization reactions, to form co-polymers, enhance cross-linking, or to act as polymer stabilizers.

[0087] In various applications, it is desirable to vector or target a fullerene to particular environments, e.g., for application in biological systems. For example, the target can be a dermal or other membrane surface or organ. The present invention provides a convenient means to synthesize new molecules with chemical functionalities for such vectoring. Examples include but are not limited to the formation of lipophilic, hydrophilic, amphiphilic, or bio-site specific (enzyme or antibodies) compounds. For example, compound 4 is lipophilic, and could be used to vector a fullerene to lipophilic environments, such as cell membranes, and/or to pass through cell membranes, and/or to penetrate the stratum corneum of the skin through the lipophilic phases of mammalian skin. The compound can be delivered to the target in a carrier vehicle. Suitable carrier vehicles include those typically employed in the dermal application of pharmaceutical and cosmetic materials.

[0088] As another example, a more highly hydrophilic moiety could be attached as in compound 5 (or a poly(ethylene glycol), a poly(ethylene oxide), mono-, di-, or poly-saccharides, or other hydrophilic moiety for enhanced hydrophilicity) for vectoring of fullerenes to hydrophilic regions, such as in the hydrophilic phases of mammalian skin or to allow for biodistribution in the bloodstream, and/or absorption through the gastrointestinal tract. As yet another example, an amphiphilic molecule can be conveniently synthesized by attaching a hydrophilic moiety at the X position and a lipophilic moiety at the Y position in compound 1 or vice versa, or at any of the alternative points of substitution in compounds 7 or 9.

[0089] Any constituent for vectoring, including the hydro- and lipophilic moieties above, or any other such moieties, may be substituted at any of the substitution positions in compounds 1, 7 or 9, such as at X, Z, X', Y', or Z'. Alternatively, other moieties important for biological vectoring, such as but not limited to monoclonal antibodies may be substituted at X, Z, X', Y', or Z' in compounds 1, 7 or 9.

[0090] Likewise, other chemical or physical functionalities may be added to a fullerene radical scavenging molecule by substitution at X, Z, X', Y', or Z' in compounds 1, 7 or 9, such as the following:

- [0091] 1. Enhanced solubility in media such as oils, alcohols, water, or aromatics, etc.;
- [0092] 2. Additional chemical reactivity, for example, the addition of other radical scavenging moieties, such as other antioxidants (e.g., carotenoids, flavinoids, anthocyanidins, lipoic acids, ubiquinoids, retinoids), for the formation of combination antioxidants in the form of molecular dyads,
- [0093] 3. Enhanced radical scavenging efficacy against a given radical, or to provide an effective multi-functional radical scavenger effective against different radicals (e.g., β-carotene, an efficient scavenger of singlet oxygen, but not of peroxy, substituted at X, Z, X', Y', or Z' in compounds 1, 7 or 9 to provide a single radical scavenging molecule effective against both singlet oxygen and peroxy, against which fullerenes are effective);
- [0094] 4. For the formation of co-polymers to scavenge radicals in radical polymerization reactions, to form co-polymers, enhance cross-linking, or to act as polymer stabilizers;

[0095] 5. The modification of physical properties, such as enhanced optical absorption;

[0096] 6. To quench the singlet excited state of the fullerenes so that intersystem crossing to the excited triplet state of the fullerene does not occur and thus singlet oxygen is not generated.

[0097] The molecules of the instant invention can be used in compositions which contain these molecules, such as, but not limited to, salts of the molecules of the instant invention; formulations containing molecules of the instant invention, including but not limited to compositions used in personal care, such as oil/water or water/oil emulsions; liposomal formulations, etc.; host-guest inclusions such as cyclodextrin complexes, etc.

[0098] The molecules of the present invention may be used in compositions with other reactive compounds, in particular in combination with other radical scavengers, such as tocopherols, ascorbates, ubiquinone, carotenoids, anthocyanidins, flavinoids, lipoic acids, etc. Fullerene molecules of the present invention may provide synergistic chemical effects, whereby the fullerene enhances or preserves the efficacy of one or more of the other substituent radical scavengers of the composition. Also, it is contemplated that the fullerenes described herein can be used to vector another radical scavenger such as those mentioned here by chemical substitution of the radical scavenger at X, Z, X', Y', or Z' in compounds 1, 7 or 9 above, to various environments, and/or preserve or enhance the efficacy in various environments. The fullerenes of the present invention may also be used in combination with other formulation agents such as stabilizers, surfactants, emulsifiers, preservative agents, UV absorbing agents, anti-inflammatory agents, or anti-microbial agents.

EXAMPLE 1

[0099] Tests were conducted to study the effectiveness of methanofullerene derivatives against radicals present in cigarette smoke (predominantly peroxy radical). The cigarette smoke was bubbled through a glass frit into a solvent (decalin) in which radical scavengers were dissolved. The smoke then exited this solvent and was passed through a second flask, in which a fluorescent probe that fluoresces upon oxidation by radicals was used (Dihydrorhodamine 6G (DHR 6G), purchased from Molecular Probes). See FIG. 5. The variation of fluorescent signal corresponds directly to the radical content of the cigarette smoke, and thus a measure of the reduction of radicals by the radical scavenger is measured. Signals were measured every 10 seconds. FIG. 6A shows a comparison of the fluorescent signal measured under identical conditions for Molecule A, i.e., PCBM (compound 3), and Vitamin E, a commonly used radical scavenger, and also known to be effective against peroxy radical.

[0100] It can be seen that PCBM clearly scavenges significantly more of the radicals present in the cigarette smoke than Vitamin E. Since peroxy radicals are the major radical species present in cigarette smoke, molecules of the instant invention are also effective to prevent oxidative damage in biological systems, where peroxy radical oxidation is a major pathway in lipid peroxidation. Hydroxyl radical is also present in cigarette smoke, and likewise is an important cause of oxidative stress in biological systems.

EXAMPLE 2

[0101] Tests were conducted to study the sensitivity of the test apparatus in Example 1 to varying concentrations of Vitamin E as a radical scavenger to scavenge radicals present in cigarette smoke (predominantly peroxy radical). The cigarette smoke was bubbled through a cylindrical, coarse glass frit into a solvent (decalin) in which radical scavengers were dissolved. The smoke then exited this solvent and was passed through a second flask, in which a fluorescent probe that fluoresces upon oxidation by radicals was used (Dihydrorhodamine 6G (DHR 6G), purchased from Molecular Probes). See FIG. 6B. The variation of fluorescent signal corresponds directly to the radical content of the cigarette smoke, and thus a measure of the reduction of radicals by the radical scavenger is measured. Signals were measured every 10 seconds. FIG. 6B shows a comparison of the fluorescent signal measured under identical conditions for 150 μ M and 300 μ M Vitamin E, a commonly used radical scavenger, and also known to be effective against peroxy radical. It can be clearly seen that doubling the Vitamin E concentration from 150 μ M to 300 μ M gives a very small deflection. The difference in fluorescence signal between 300 μ M PCBM and 300 μ M Vitamin E thus corresponds to a very large difference in radical scavenging efficiency.

EXAMPLE 3

[0102] Synthesis of PCB-C18 ([6,6]-phenyl C₆₁-butyric acid octadecyl ester) by transesterification of PCBM is described.

[0103] A mixture of 1.90 g of PCBM (compound 3), 6.0 g of 1-octadecanol, 250 mg of dibutyltin oxide, and 50 mL of ortho-dichlorobenzene was heated at 80° C. under an N₂ atmosphere for 3 days. The reaction was cooled down and the crude product was isolated by column chromatography (silica gel; cyclohexane/toluene=1:1 (v/v) as eluent). The crude fullerene derivative was then further purified by a second column chromatography (silica gel; cyclohexane/toluene=1:1 (v/v) as eluent). The fractions that were >99% purity (HPLC analysis) were combined and concentrated in vacuo. The residue was redissolved in ortho-xylene, the fullerene derivative was precipitated with methanol, and isolated by centrifugation. The precipitate was washed repeatedly with methanol and small portions of pentane, each time precipitating the material by centrifugation. After drying in vacuo, 822 mg of PCB-C18 was obtained.

EXAMPLE 4

[0104] Synthesis of PCB-C12 (compound 4) by transesterification of PCBM is described.

[0105] A mixture of 1.83 g of PCBM (compound 3), 4.6 g of 1-dodecanol, 148 mg of dibutyltin oxide, and 20 mL of ortho-dichlorobenzene was heated at 80° C. under an N₂ atmosphere for 24 hours. The reaction was cooled down and the product was isolated by column chromatography (silica gel; cyclohexane/toluene=1:1 (v/v) as eluent). The fractions containing PCB-C12 were combined and concentrated in vacuo. The resulting material was redissolved in 15 mL of chlorobenzene, the fullerene derivative was precipitated with methanol, and isolated by centrifugation. The precipitate was washed with methanol and dried in vacuo. This procedure of washing and drying was repeated once. The

product was then redissolved in 20 mL of chloroform, precipitated with methanol, and isolated by centrifugation. The precipitate was washed with methanol and dried in vacuo. This gave 1.58 g of PCB-C12 (compound 4) as a fine, black powder.

EXAMPLE 5

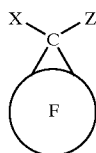
[0106] Synthesis of PCB-EO4 (compound 5) by transesterification of PCBM is described.

[0107] A mixture of 182 mg of PCBM (compound 3), 2.0 mL of tetraethylene glycol, 11 mg of dibutyltin oxide, and 5 mL of ortho-dichlorobenzene was heated at 95° C. under an N₂ atmosphere for 3 days. The reaction was cooled down and the crude product was isolated by column chromatography (silica gel; chloroform as eluent). It was then further purified by a second column chromatography (silica gel; first chloroform/ethyl acetate (95:5 (v/v)), then chloroform/ethyl acetate (9:1 (v/v)), then chloroform/ethyl acetate (4:1 (v/v)) as eluent). The fractions containing the product were combined and concentrated in vacuo. The resulting material was redissolved in 15 mL of toluene, precipitated with methanol, washed with methanol, and dried in vacuo. Subsequently, the fullerene derivative was washed once more with methanol and dried again in vacuo. This gave 105 mg of PCB-EO4 (compound 5).

What is claimed is:

1. A method of scavenging free radicals in or on a target, comprising:

exposing a target to a compound having the formula,



where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is (C')(R')_n and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and

where Z is (C'')(R'')_n and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and n=1, 2, or 3, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitriles, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates.

2. The method of claim 1, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is (C'')(R'')_n and C'' is a carbon atom selected from the group

consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group.

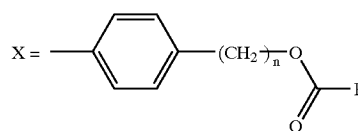
3. The method of claim 1, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is (C'')(R'')_n and C'' is an alkyl carbon and R'' is independently selected from the group consisting of alkyl moieties and alkyl moieties bearing a hetero or functional group.

4. The method of claim 3, wherein Z is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 8 carbons.

5. The method of claim 3, wherein Z is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 12 carbons.

6. The method of claim 3, wherein Z is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 16 carbons.

7. The method of claim 3, 4, 5, or 6, wherein:



where n is in the range of 1 to 20, and R is any chemical group.

8. The method of claim 1, 2 or 3, wherein the compound comprises two to four C(X)(Z) adducts on the fullerene ring.

9. The method of claim 1, 2 or 3, wherein the fullerene comprises from about 60 to about 120 carbon atoms.

10. The method of claim 1, 2 or 3, wherein the fullerene compound comprises a [5,6] fulleroid.

11. The method of claim 1, 2 or 3, wherein the fullerene compound comprises a [6,6] methanofullerene.

12. The method of claim 1, wherein X and Z are different.

13. The method of claim 1, wherein one or more of X and Z comprises a lipophilic moiety.

14. The method of claim 13, wherein the lipophilic moiety is selected from the group consisting of fatty acids, fatty amides, fatty alcohols, and fatty amines.

15. The method of claim 13, wherein the compound is capable of transport through lipid phases in a biological system.

16. The method of claim 1, wherein one or more of X and Z comprises a hydrophilic moiety.

17. The method of claim 16, wherein the compound is capable of transport through aqueous phases in a biological system.

18. The method of claim 1, wherein one or more of X and Z comprises a chemical moiety that is independently effective as a free radical scavenger.

19. The method of claim 1, wherein one or more of X and Z comprises an amphiphilic moiety.

20. The method of claim 1, wherein X=X' and Z=(A)(C'=Q')(Z')(Y'), and

where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl;

A is an aliphatic group containing 1 to 20 carbon atoms;

Q' is O, N or S;

Z' is halogen, O, N, or S; and Z' is bound to C' and

Y' is any chemical group bound to Z';

or any salts thereof.

21. The method of claim 20, wherein the fullerene comprises from about 60 to about 120 carbon atoms.

22. The method of claim 20, wherein the fullerene compound comprises a [5,6] fulleroid.

23. The method of claim 20, wherein the fullerene compound comprises a [6,6] methanofullerene.

24. The method of claim 20, wherein A contains 3 to 12 carbon atoms.

25. The method of 20, wherein Z' and Q' are O.

26. The method of claim 25, wherein Y' is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 8 carbons.

27. The method of claim 25, wherein Y' is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 12 carbons.

28. The method of claim 25, wherein Y' is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 16 carbons.

29. The method of claim 20, wherein Y' is a chemical moiety that is independently effective as a free radical scavenger.

30. The method of claim 20, wherein Y' is an amphiphilic moiety.

31. The method of claim 20, wherein Y' is selected from the group consisting of sugars, histamines, amino acids and carotenoids.

32. The method of claim 20, wherein $-(C'=Q')(Z')(Y')$ in combination comprises a carboxylic acid (or carboxylate), ester, amide, anhydride, acid halide, lactone, or lactam species.

33. The method of claim 20, wherein the compound comprises [6,6]-phenyl C_{61} -butyric acid methyl ester (PCBM).

34. The method of claim 20, wherein the compound comprises two or more adducts of $C(X)((A)(C'=Q')(Z')(Y'))$ with the fullerene ring.

35. The method of claim 1, 2, 3 or 20, further comprising:

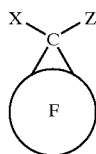
exposing the target to at least one additional radical scavenging compound.

36. The method of claim 1, 2, 3 or 20, wherein the compound further comprises:

an additive selected to enhance or preserve the efficacy of the compound.

37. A method of altering radical mediated chemical pathways in a biological system, comprising:

reacting a radical species present in a biological system with a compound having the formula,



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where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and

where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and n=1, 2, or 3, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitrites, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

38. The method of claim 37, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group.

39. The method of claim 37, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is an alkyl carbon and R'' is independently selected from the group consisting of alkyl and alkyl moieties bearing any hetero or functional group.

40. A The method of claim 37, wherein $X=X'$ and $Z=(A)(C'=Q')(Z')(Y')$, and where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl;

A is an aliphatic group containing 1 to 20 carbon atoms;

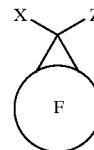
Q is O, N or S;

Z' is halogen, O, N, or S; and Z' is bound to C'; and

Y' is any chemical group bound to Z';

or any salts thereof.

41. A method of reducing oxidative stress in a biological system, comprising: reacting a radical species present in a biological system with a compound having the formula,



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where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and

where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitriles, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

42. The method of claim 41, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group.

43. The method of claim 41, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is an alkyl carbon and R'' is independently selected from the group consisting of alkyl and substituted alkyl moieties.

44. The method of claim 41, wherein $X=X'$ and $Z=(A)(C'=Q')(Z')(Y')$, and where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl;

A is an aliphatic group containing 1 to 20 carbon atoms;

Q' is O, N or S;

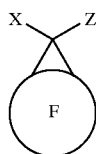
Z' is halogen, O, N, or S; and Z' is bound to C' ; and

Y' is any chemical group bound to Z';

or any salts thereof.

45. A method of preventing or reducing lipid peroxidation in a biological system, comprising:

exposing a biological system to a compound having the formula,



where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and

where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitriles, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

aldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

46. The method of claim 45, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group.

47. The method of claim 45, wherein C' is an aryl carbon and X is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl moieties and Z is $(C'')(R'')_n$ and C'' is an alkyl carbon and R'' is independently selected from the group consisting of alkyl and substituted alkyl moieties.

48. The method of claim 45, wherein $X=X'$ and $Z=(A)(C'=Q')(Z')(Y')$,

where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl;

A is an aliphatic group containing 1 to 20 carbon atoms;

Q' is O, N or S;

Z' is halogen, O, N, or S; and Z' is bound to C' ; and

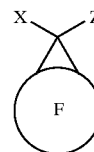
Y' is any chemical group bound to Z';

or any salts thereof.

49. A composition, comprising:

a biologically compatible carrier; and

a compound having the formula,



where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, and

where Z is $(C'')(R'')_n$ and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and $n=1, 2, \text{ or } 3$, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitriles, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

50. The composition of claim 49, wherein $X=X'$ and $Z=(A)(C'=Q')(Z')(Y')$,

where X' is selected from the group consisting of aryl group, substituted aryl group, a heteroaryl and a substituted heteroaryl;

A is an aliphatic group containing 1 to 20 carbon atoms;

Q' is O, N or S;

Z' is halogen, O, N, or S; and Z' is bound to C'; and

Y' is any chemical group bound to Z';

or any salts thereof.

51. The composition of claim 49, wherein the carrier is selected for application to the skin.

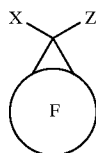
52. The composition of claim 49, wherein X or Z is selected for application to the skin and delivery in the stratum comeum or through the stratum comeum to deeper layers of the skin.

53. The composition of claim 49, wherein the compound does not penetrate the stratum comeum to any appreciable degree.

54. The composition of claim 53, wherein X or Z comprises a polymer.

55. The method of claim 1, where X or Z comprises a polymer.

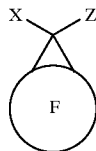
56. A compound, comprising:



wherein the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

wherein X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties and Z contains a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons.

57. A compound, comprising:



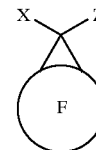
wherein the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is (C')(R')_n and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and

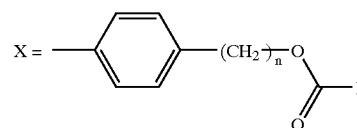
wherein Z contains O(CH₂CH₂O)_mCH₂CH₂OP, where P is H or alkyl or aryl, and m is in the range of 1 to 100.

58. The compound of claim 57, wherein X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties

59. A compound, comprising:



wherein the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,



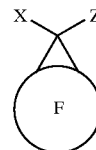
where R is any chemical group, and n is in the range of 1 to 20; and

where Z is (C'')(R'')_n and C'' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons and R'' is independently selected such that Z is a non-electron withdrawing group, and n=1, 2, or 3, or Z is an electron-withdrawing group selected from the group consisting of aldehydes, ketones, esters, anhydrides, nitrites, amides, thioaldehydes, thioketones, thioesters, amidate esters, isocyanides, isocyanates, isothiocyanates, sulfones, sulfonates, and the like.

60. The compound of claim 59, wherein R is alkyl.

61. The compound of claim 59, wherein R is a linear or branched, saturated or unsaturated hydrocarbon moiety having at least 7 carbons.

62. A composition, comprising:

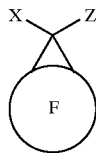


wherein where the ring, F, comprises a fullerene comprising from about 20 to about 240 carbon atoms,

where X is (C')(R')_n and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and Z contains a radical scavenging moiety selected from the group consisting of carotenoids, flavonoids, anthocyanidins, lipoic acids, ubiquinoids, and retinoids.

63. The composition of claim 62, wherein X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties.

64. A composition, comprising:



where X is $(C')(R')_n$ and C' is a carbon atom selected from the group consisting of alkyl, alkenyl, alkynyl, and aromatic carbons, R' is independently selected such that X is a non-electron withdrawing group, and n=1, 2, or 3, and

wherein Z contains $O(CH_2CH_2CH_2O)_mCH_2CH_2CH_2OP$, where P is H or alkyl or aryl, and m is in the range of 1 to 100.

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65. The compound of claim 64, wherein X is selected from the group of aryl, substituted aryl, heteroaryl and substituted heteroaryl moieties.

66. The method of transesterification of a fullerene derivative containing a carboxylic ester anywhere in any substituent or any number thereof, using dibutyltin oxide as the catalyst for the transesterification reaction, with or without the use of a cosolvent or solvent to increase the solubility of the fullerene derivative in the reaction mixture.

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