The invention relates to compounds represented by the general formula (I): and pharmaceutically acceptable salts thereof, wherein \( i \) is an integer from 1 to 5; \( p \) is an integer from 0 to 4; \( R_i \) is selected from the group consisting of a hydroxyl group, an alkoxy group, a thiol group, and a thiocarbonylthio group; \( R_2 \) and \( R_3 \) are independently a methylene group or a nucleophile, with the proviso that at least one of \( R_2 \) and \( R_3 \) is a nucleophile group; \( Z \) is an oxygen (O) atom or sulfur (S) atom; \( T \) is hydrogen or an optionally substituted aliphatic group; with the proviso that when \( n = 2 \), \( R_i \) is not -OCH\(_3\) on the carbon-3 position of the phenyl group and \( R_i \) is not -OH on the carbon-4 position of the phenyl group.

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(54) Title: NOVEL COMPOUNDS AND USES THEREOF

(57) Abstract: The invention relates to compounds represented by the general formula (I): and pharmaceutically acceptable salts thereof, wherein \( i \) is an integer from 1 to 5; \( p \) is an integer from 0 to 4; \( R_i \) is selected from the group consisting of a hydroxyl group, an alkoxy group, a thiol group, and a thiocarbonylthio group; \( R_2 \) and \( R_3 \) are independently a methylene group or a nucleophile, with the proviso that at least one of \( R_2 \) and \( R_3 \) is a nucleophile group; \( Z \) is an oxygen (O) atom or sulfur (S) atom; \( T \) is hydrogen or an optionally substituted aliphatic group; with the proviso that when \( n = 2 \), \( R_i \) is not -OCH\(_3\) on the carbon-3 position of the phenyl group and \( R_i \) is not -OH on the carbon-4 position of the phenyl group.
NOVEL COMPOUNDS AND USES THEKEOF

Technical Field

The present invention generally relates to novel compounds, including capsaicin analogues and derivatives thereof, which have anti-oxidative activity, and to their use in medicine, health care, cosmetics and food.

Background

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the main component in plants of the Capsicum genus, which include chili peppers, red peppers and paprika. Capsaicin comprises a class of compounds that have a lipophilic alkyl chain that is connected, via an amide linkage, to a vanillyl group with a polar hydroxyl group.

Capsaicin exhibits anti-oxidative activity and can thus act as an anti-oxidant. Anti-oxidants are substances that slow or prevent the oxidative process caused by unstable oxidant (or oxidizing) molecules, such as free radicals or reactive oxygen species. The biological state in which the production of such oxidant molecules by bodily- systems or external sources overwhelms the natural anti-oxidative capacity is known as 'oxidative stress'. Oxidative stress can lead to cellular and tissue damage, and has been implicated as a contributory factor in many diseases and age-related disorders, for example, heart disease, macular degeneration, diabetes, cancer, and inflammatory disorders.

Other than health related implications, such oxidative processes can lead to deterioration in the
quality of products such as food, cosmetics and personal care products. For example, the oxidative processes can cause the development of rancidity and odour as well as discolouration of these products.

Commercial production of capsaicin currently involves isolation of the compound from the plant raw material. Hence, commercial production of capsaicin is currently dependent on the quality, quantity and price of the crop. As capsaicin is only present in the plant in small quantities, isolation of the compound from the plant raw material is difficult and costly.

Other commercial anti-oxidants such as the synthetic chemicals butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are volatile and decompose easily at high temperatures. Animal studies have also shown that BHT causes undesirable suppression of liver enzymes and enlargement of the liver.

Therefore, there is a need to provide anti-oxidative agents that overcome or at least ameliorate one or more of the disadvantages described above.

There is a need to provide anti-oxidative agents, such as novel capsaicin analogues and derivatives thereof, that exhibit potent anti-oxidative properties and reduced or no cytotoxic effects, and that can be easily produced in large quantities at low cost.

There is a need to provide novel capsaicin analogues and derivatives thereof for use in a medicament to treat and/or prevent oxidative stress related disorders, which have sufficiently low cytotoxicity such that they are not harmful to humans.
There is a need to provide novel capsaicin analogues and derivatives thereof for use as stabilizers in food, cosmetics and personal care products.

**Summary**

According to a first aspect, there is provided a compound represented by the general formula (I):

\[
\begin{align*}
\text{R}_{2} & \text{R}_{3} \text{T} \\
\text{Z} & \\
\text{nR}_{1} & \\
\end{align*}
\]

and pharmaceutically acceptable salts thereof, wherein

- \( n \) is an integer from 1 to 5;
- \( p \) is an integer from 0 to 4;
- \( R_{i} \) is selected from the group consisting of a hydroxyl group, an alkoxy group, a thiol group, and a thioether group;
- \( R_{2} \) and \( R_{3} \) are independently a methylene group or a nucleophile, with the proviso that at least one of \( R_{2} \) and \( R_{3} \) is a nucleophile group;
- \( Z \) is an oxygen (O) atom or sulfur (S) atom;
- \( T \) is hydrogen or an optionally substituted aliphatic group;
with the proviso that when $n = 2$, $R_i$ is not $-\text{OCH}_3$ on the carbon-3 position of the phenyl group and $R_i$ is not $-\text{OH}$ on the carbon-4 position of the phenyl group.

According to a second aspect, there is provided a pharmaceutical or cosmetic composition comprising an active ingredient a compound of formula (I) as defined herein and a pharmaceutically or cosmetically acceptable carrier.

According to a third aspect, there is provided a food preparation comprising a compound of formula (I) as defined herein.

According to a fourth aspect, there is provided a compound of formula (I) as defined herein for use in the prevention and/or treatment of a condition associated with oxidative stress and/or a condition caused by presence of free radicals.

According to a fifth aspect, there is provided use of a compound of formula (I) as defined herein, in the manufacture of a medicament for the prevention and/or treatment of a condition associated with oxidative stress and/or a condition caused by presence of free radicals.

According to a sixth aspect, there is provided a method of preventing and/or treating a condition in a subject, wherein the condition is associated with oxidative stress and/or caused by presence of free radicals, the method comprising administering to the subject an effective amount of a compound of Formula (I) as defined herein, or a pharmaceutically-acceptable salt thereof.
Definitions

The following are some definitions that may be helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for a better understanding of the following description.

Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

Those skilled in the art will also appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

The term "analogue" refers to a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the chemical and/or biological activities that are characteristic of the specific compound and class. For example, the term "analogue" as used herein may be used to refer to a chemically modified form of a compound of...
formula (I) which maintains the anti-oxidant properties of a compound of formula (I).

The term "derivative" refers to any salt, solvate or prodrug, e.g. ester, of a compound of the invention, which upon administration to a subject, is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Preparation of such derivatives is routine to those skilled in the art without undue experimentation.

The term "active compound" in connection with the present invention is understood as meaning a compound as disclosed herein which is capable of causing a required therapeutic or cosmetic effect in a patient or subject, for example an anti-oxidant effect.

The terms "pharmaceutically acceptable salt" and "cosmetically acceptable salt" refer to those salts which retain the chemical and/or biological effectiveness and properties of the active compound, which are not otherwise undesirable. A thorough discussion of pharmaceutically and cosmetically acceptable salts is available in Remington's Pharmaceutical Sciences (Mack Pub. Co., N.J. 1991).

The term "optionally substituted" as used herein means the group to which this term refers may be unsubstituted, or may be substituted with one or more groups independently selected from hydrogen, oxygen, sulfur, alkyl, alkenyl, alkynyl, thioalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, halo, carboxyl, haloalkyl, haloalkynyl, hydroxyl, alkoxy, thiaoalkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, amino, nitroalkyl, nitroalkenyl, nitroalkynyl,
nitroheterocyclyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, heterocycloxy, heterocycloamino, haloheterocycloalkyl, alkylsulfonyl, alkylcarbonyloxy, alkylthio, acylthio, phosphorus-containing groups such as phosphonyl and phosphinyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, cyano, cyanate, isocyanate, \(-\text{C}(\text{O})\text{NH} (\text{alkyl})\), and \(-\text{C}(\text{O'})\text{N} (\text{alkyl})_2\).

The term "hydroxyl" as used herein refers to the functional group \(-\text{OH}\).

The term "alkoxy" as used herein refers to straight chain or branched alkyloxy groups. Examples include methoxy, ethoxy, \(\text{n-propoxy}\), \(\text{isopropoxy}\), \(\text{tert-butoxy}\), and the like.

The term "thiol" means \(-\text{SH}\).

The term "thioether" refers to ether groups wherein the oxygen is replaced with a sulfur. The thioether groups include but are not limited to \(-\text{alkylene-S-alkyl}\), \(-\text{alkylene-S-aryl}\), \(-\text{alkylene-S-arylalkyl}\), \(-\text{alkylene-S-alkylaryl}\), \(-\text{aryl-S-alkyl}\), \(-\text{aryl-S-aryl}\), \(-\text{aryl-S-arylalkyl}\), \(-\text{aryl-S-alkylaryl}\), \(-\text{aryl-S-alkylaryl}\), \(-\text{alkyl-S-alkyl}\), \(-\text{alkyl-S-aryl}\), \(-\text{alkyl-S-alkylaryl}\), and \(-\text{alkyl-S-arylalkyl}\). The thioether groups may be optionally substituted as described above.

The term "nucleophile" as used herein refers to a chemical moiety that has a reactive pair of electrons and that participates in a chemical reaction by donating electrons, i.e., nucleophiles are electron donor
compounds. The nucleophile may be a halogen, nitrogen, sulfur or oxygen nucleophile. Exemplary nucleophiles include fluorides, cyanides, iodides, chlorides, bromides, acetates, enolates, primary amines, secondary amines, amino, alkoxides, thiols, alkyl sulfides (such as mercaptans), hydroxides, azides, and hydrazines, among others.

The term "amino" as used herein refers to groups of the form $-\text{NR}_a$ or $-\text{NR}_a\text{R}_b$ wherein $\text{R}_3$ and $\text{R}_b$ are independently selected from the group including but not limited to hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy and optionally substituted aryl groups. For example, the term "amino" as used herein may be used to refer to an $-\text{NH}$ group at the $\text{R}_2$ and/or $\text{R}_3$ position of a compound of formula (I), or to an $-\text{NHCH}_3$ group in the optionally substituted aliphatic group at the $\text{T}$ position of a compound of formula (I).

The term "aliphatic" refers to a linear, branched, or cyclic alkyl, alkenyl, or alkynyl group.

The term "alkyl" includes within its meaning straight chain or branched chain saturated aliphatic groups having from 1 to 10 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. For example, the term alkyl includes, but is not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, 2-
ethylpentyl, 3-ethylpentyl, heptyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 5-methylheptyl, 1-methylheptyl, octyl, nonyl, decyl, and the like.

The term "lower alkyl" refers to a straight or branched saturated hydrocarbon chain having 1, 2, 3, 4, 5, or 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

The term "alkenyl" includes within its meaning straight or branched chain unsaturated aliphatic hydrocarbon groups having from 2 to 10 carbon atoms, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms and having at least one double bond, of either E, Z, cis or trans stereochemistry where applicable, anywhere in the alkyl chain. Examples of alkenyl groups include but are not limited to ethenyl, vinyl, allyl, 1-methylvinyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butentyl, 1,3-butadienyl, 1-penteny, 2-penteny, 3-penteny, 4-penteny, 1,3-pentadieny, 2,4-pentadieny, 1,4-pentadieny, 3-methyl-2-butenyl, 1-hexenyl, 2-hexeny, 3-hexenyl, 1,3-hexadieny, 1,4-hexadieny, 2-methylpenteny, 1-hepteny, 2-hepteny, 3-hepteny, 1-octeny, 1-noneny, 1-deceny, and the like.

The term "lower alkenyl" refers to a straight or branched saturated hydrocarbon chain having 2, 3, 4, 5, or 6 carbon atoms.
The term "alkynyl" as used herein includes within its meaning straight or branched chain unsaturated aliphatic hydrocarbon groups having from 2 to 10 carbon atoms and having at least one triple bond anywhere in the carbon chain. Examples of alkynyl groups include but are not limited to ethynyl, 1-propynyl, 1-butynyl, 2-butynyl, 1-methyl-2-butynyl, 3-methyl-1-butynyl, 1-pentynyl, 1-hexynyl, 1-methylpentynyl, 1-heptynyl, 2-heptynyl, 1-octynyl, 2-octynyl, 1-nonyl, 1-decynyl, and the like.

The term "lower alkynyl" refers to a straight or branched saturated hydrocarbon chain having 2, 3, 4, 5, or 6 carbon atoms.

The term "heteroatom" or variants such as "hetero-" as used herein refers to oxygen (O), nitrogen (N), phosphorus (P) and sulfur (S).

The term "aryl" or variants such as "aromatic group" or "arylene" as used herein refers to single, polynuclear, conjugated and fused residues of aromatic hydrocarbons having from 6 to 10 carbon atoms. Exemplary aryl groups include, but are not limited to phenyl, naphthyl, tetrahydronaphthyl, and the like.

The term "heteroaryl" and variants such as "heteroaromatic group" or "heteroarylene" as used herein, includes within its meaning single, polynuclear, conjugated and fused aromatic moieties having 5 to 20 atoms wherein 1 to 6 atoms are heteroatoms selected from O, N, NH and S. Examples of such groups include pyridyl, 2,2'-bipyridyl, phenanthroline, quinolinyl, thiophenyl, indoyl, furanyl and pyrrolyl moieties and the like.

The term "cycloalkyl" as used herein refers to cyclic saturated aliphatic groups and includes within its
meaning monocyclic, bicyclic, polycyclic or fused polycyclic hydrocarbon moieties having from 3 to 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, 2-methylcyclopentyl, 3-methylcyclopentyl, cyclohexyl, and the like.

The term "halide" or variants such as "halogen" or "halo" as used herein refers to fluoride, chloride, bromide and iodide.

The present invention includes within its scope all isomeric forms of the compounds disclosed herein, including all diastereomeric isomers, racemates and enantiomers. Thus, compounds of formula (I) and derivatives thereof should be understood to include, for example, E, Z, cis, trans, (R), (S), (L), (D), (+), and/or (-) forms of the compounds, as appropriate in each case.

The term "oxidative stress" as used herein refers to damage to biological molecules resulting from oxidation including, but not limited to, oxidation of lipoproteins and membrane phospholipids; lipid peroxidation; protein damage, including cleavage of amino acid bonds and oxidation of functional groups; nucleic acid strand breaks; nucleic acid base modifications leading to point mutations; inhibition of RNA and protein synthesis; protein cross-linking; impaired maintenance of membrane ion gradients; and depletion of cellular levels of ATP, any of which may lead to cellular dysfunction and eventually to disease.
The term "anti-oxidative agent" or "anti-oxidant" refers to a compound having reducing or reductive activity or power, which may prevent the generation of oxidizing molecules such as free radicals and reactive oxygen species, and remove or inactivate such oxidizing molecules, thus preventing, delaying or minimizing oxidative stress, and the damage and deterioration resulting therefrom. Typically, such anti-oxidative agents remove or inactivate the oxidizing molecules by means of electron transfer from the anti-oxidative agent to the oxidizing molecule. Anti-oxidative agents disclosed herein have applications in the treatment of one or more oxidative stress related disorder as described below, and in prevention of deterioration in product quality (such as in food, cosmetic and personal care products). Deterioration in product quality may be for example, development of rancidity and undesirable colour and odour.

The term "treatment" includes any and all uses which remedy a disease state or symptoms, prevent the establishment of disease, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever. Hence, "treatment" includes prophylactic and therapeutic treatment.

The term "patient" or "subject" refers to patients or subjects of human or other mammal and includes any individual it is desired to examine or treat using the active compounds and methods disclosed herein. However, it will be understood that "patient" or "subject" does not imply that symptoms are present. Suitable mammals
that fall within the scope of the invention include, but are not restricted to, primates, livestock animals (e.g. sheep, cows, horses, donkeys, pigs), laboratory test animals (e.g. rabbits, mice, rats, guinea pigs, hamsters), companion animals (e.g. cats, dogs) and captive wild animals (e.g. foxes, deer, dingoes). "Mammal" refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, and pet companion animals such as a household pet and other domesticated animal such as, but not limited to, cattle, sheep, ferrets, swine, horses, poultry, rabbits, goats, dogs, cats and the like. Preferred companion animals are dogs and cats. Preferably, the mammal is human.

The term "administering" and variations of that term including "administer" and "administration", includes contacting, applying, delivering or providing a compound or composition of the invention to an organism, or a surface by any appropriate means.

The term "effective amount" when used in relation to an anti-oxidative agent, refers to an amount sufficient to effect the desired anti-oxidative benefit. Similarly, the terms "therapeutically effective amount," "pharmacologically effective amount" and "cosmetically effective amount" include within their meanings a sufficient but non-toxic amount of a compound or composition of the invention to provide the desired therapeutic or cosmetic effect. The exact amount required will vary from subject to subject depending on factors such as the species being treated, the age and general condition of the subject, the severity of the
condition being treated, the particular agent being administered, the mode of administration, and so forth. Thus, it is not possible to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

The term "dosage unit form" as used herein refers to physically discrete units suited as unitary dosages for the individual to be treated; each unit containing a predetermined quantity of compound (s) is calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The compound (s) may be formulated for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in an acceptable dosage unit. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the ingredients.

Unless specified otherwise, the terms "comprising" and "comprise", and grammatical variants thereof, are intended to represent "open" or "inclusive" language such that they include recited elements but also permit inclusion of additional, unrecited elements.

As used herein, the term "about", in the context of concentrations of components of the formulations, typically means +/- 5% of the stated value, more typically +/- 4% of the stated value, more typically +/- 3% of the stated value, more typically, +/- 2% of the stated value, even more typically +/- 1% of the stated
value, and even more typically +/- 0.5% of the stated value.

Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Certain embodiments may also be described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

**Detailed Disclosure of Embodiments**

Exemplary, non-limiting embodiments of the active compounds having anti-oxidative activity will now be disclosed.
The inventors have found that the active compounds disclosed herein exhibit potent anti-oxidative activity with reduced or no cytotoxicity. Accordingly, the active compounds disclosed herein can be used as anti-oxidative agents in medicaments and health supplements to treat and/or prevent diseases or conditions associated with oxidative stress and/or caused by presence of free radicals, and in cosmetic products to produce an anti-oxidative effect for example an anti-aging effect. The active compounds disclosed herein can also be used as anti-oxidative agents to stabilize food, cosmetic and personal care products against deterioration.

**The Active Compounds**

The active compounds may be represented by a compound having the general formula (I):

![Chemical Structure](image)

and pharmaceutically acceptable salts thereof, wherein

- $n$ is an integer from 1 to 5;
- $p$ is an integer from 0 to 4;
- $R_i$ is selected from the group consisting of a hydroxyl group, an alkoxy group, a thiol group, and a thioether group;
R₂ and R₃ are independently a methylene group or a nucleophile, with the proviso that at least one of R₂ and R₃ is a nucleophile group;

Z is an oxygen (O) atom or sulfur (S) atom;

T is hydrogen or an optionally substituted aliphatic group;

with the proviso that when n = 2, Rᵢ is not -OCH₃ on the carbon-3 position of the phenyl group and R₁ is not -OH on the carbon-4 position of the phenyl group.

n can be 1, 2, 3, 4 or 5.

In one embodiment, Z is an oxygen (O) atom.

In another embodiment, Z is not a sulfur (S) atom.

Advantageously, in embodiments where Z is an oxygen (O) atom instead of a sulfur (S) atom, the compounds of formula (I) exhibit high anti-oxidant activity and reduced or no cytotoxicity.

In one embodiment, n is between 1 to 3.

In a preferred embodiment, n is 2. In one embodiment where n is 2, Rᵢ is on the carbon-3 position and the carbon-4 position of the phenyl group. In another embodiment where n is 2, Rᵢ is on the carbon-2 position and the carbon-5 position of the phenyl group.

In one embodiment where n is 2, each of Rᵢ is -OH. Preferably, in embodiments where n is 2 and each of Rᵢ is -OH, one of Rᵢ is on the carbon-3 position and the other Rᵢ is on the carbon-4 position of the phenyl group.

In one embodiment, Z is an oxygen (O) atom, n is 2, and each of Rᵢ is -OH.

In one embodiment, Z is not a sulfur (S) atom, n is 2, and each of Rᵢ is -OH.
In one embodiment, \( n \) is 1 and \( R_i \) is on the carbon-4 position of the phenyl group. In another embodiment where \( n \) is 1, \( R_i \) is on the carbon-2 position of the phenyl group.

\[ p \text{ can be 0, 1, 2, 3 or 4.} \]

In one embodiment, \( p \) is 1.

In one embodiment, \( R_i \) is \( \text{O}_{3} \) wherein \( U \) is an alkyl group having from 1 to 6 carbon atoms.

In another embodiment, \( R_i \) is \( \text{ZI}_i \), wherein \( \text{ZI} \) is a sulfur \((S)\) atom or oxygen \((O)\) atom and \( T_i \) is a lower alkyl group. The lower alkyl may have from 1 to 6 carbon atoms.

In yet another embodiment, \( R_i \) is independently selected from the group consisting of -OH, -OCH\(_3\), -OCH\(_2\)CH\(_3\), -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), -SH, -SCH\(_3\), -SCH\(_2\)CH\(_3\), -SCH\(_2\)CH\(_2\)CH\(_3\), -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) and -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\).

In some embodiments where \( n \) is 2, 3, 4 or 5, all the \( R_i \) groups are the same. For example, where \( n \) is 2, both \( R_i \) groups may be -OH, both \( R_i \) groups may be -OCH\(_3\), both \( R_i \) groups may be OCH\(_2\)CH\(_3\), both \( R_i \) groups may be -OCH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -OCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -SCH\(_3\), both \( R_i \) groups may be -SCH\(_2\)CH\(_3\), both \( R_i \) groups may be -SCH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), both \( R_i \) groups may be -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), or both \( R_i \) groups may be -SCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\).

In other embodiments where \( n \) is 2, 3, 4 or 5, each \( R_i \) group is different. For example, where \( n \) is 2, one \( R_i \) group may be -OH and the other \( R_i \) group may be -
OCH2CH2CH3, or where n is 3, two R1 groups may be -OH and
the third R1 group may be -OCH3 or the first R1 group may
be -OH, the second R1 group may be -OCH3 and the third R1

group may be -OCH2CH2CH3.

In one embodiment, n is 2 and one of R1 is -OH and
the other of R1 is -OCH3.

In one embodiment, T is an aliphatic group with 1 to
20 carbons. In a preferred embodiment, T is an aliphatic
group with 1 to 10 carbons. In a more preferred
embodiment, T is an aliphatic group with 5 to 10 carbons.

In one embodiment, the aliphatic group of T is an
alkyl, preferably a lower alkyl. The alkyl may be
straight chain alkyl or a branched chain alkyl.
Preferably, the alkyl is a straight chain alkyl. The
alkyl may be -CH3, -CH2CH3, -CH2CH2CH3, -CH2CH2CH2CH3,
-CH2CH2CH2CH2CH3, -CH2CH2CH2CH2CH2CH3, -CH2CH2CH2CH2CH2CH2CH3,
-CH2CH2CH2CH2CH2CH2CH2CH3 or -CH(CH3)2.

In another embodiment, the aliphatic group of T is
an aliphatic group containing at least one unsaturated
alkenyl or alkynyl group, preferably lower alkenyl or
lower alkynyl groups. Suitable alkenyl groups include
-CHCH2, -CH2CHCH2, -CHCHCH3, and -CHCHCH3, while suitable
alkynyl groups include -CCCH3, -CH2CCH, -CH2CH2CCH, -
CH2CH2CH2CCH, -CH2CH2CH2CH2CCH, and -CH2CCCH3.

In yet another embodiment, T is an aliphatic group
substituted with one or more heteroatom groups. Suitable
heteroatom groups include, without limitation, oxygen
(O), sulfur (S), and nitrogen (N) and phosphorous (P).

In yet another embodiment, T is an aryl group,
heteroaryl group or cycloalkyl group, each optionally
substituted with one or more groups selected from hydrogen, oxygen, sulfur, alkyl, alkenyl, alkynyl, thioalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, halo, carboxyl, haloalkyl, haloalkynyl, hydroxyl, alkoxy, thioalkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, amino, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroheterocyclyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, heterocycloxy, heterocycloamino, haloheterocycloalkyl, alkylsulfenyl, alkylcarbonyloxy, alkylthio, acylthio, phosphonyl, phosphinyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, cyano, cyanate, isocyanate, -C(O)NH(alkyl), and -C(0)N(alkyl).

In one embodiment, both R₂ and R₃ are methylene groups. In another embodiment, one of R₂ and R₃ is a methylene group and the other is a nucleophile. In yet another embodiment, both R₂ and R₃ are nucleophiles.

In one embodiment, the nucleophile of R₂ and/or R₃ is selected from the group consisting of a halide, a nitrogen nucleophile, a sulfur nucleophile and an oxygen nucleophile.

Suitable halides include, but are not limited to, fluoride, chloride, bromide and iodide, and the like.

Suitable nitrogen nucleophiles include, but are not limited to, amino groups (e.g. primary amino groups, secondary amino groups and tertiary amino groups), and azides (e.g. metal azides of Li, Na or K), and the like.

Suitable sulfur nucleophiles include thiols and alkyl sulfides, and the like.
Suitable oxygen nucleophiles include acetates, enolates, alkoxides, and hydroxides, and the like.

The halide, nitrogen nucleophile, sulfur nucleophile and oxygen nucleophile may be optionally substituted as described above.

In one embodiment of the compounds described herein, the nucleophile of \( R_2 \) and/or \( R_3 \) is a nitrogen nucleophile.

In one embodiment, the nitrogen nucleophile is an amino group. The amino group may be a NH group, a NHV group or a NW group where V and V are each independently selected from the group consisting of a C1-C4 lower alkyl, a phenyl, and an alkoxy group.

In one embodiment, the compound has the formula (II):

![Formula II](image)

In one embodiment, the compound has the formula (III):

![Formula III](image)

In one embodiment, the compound has the formula (IV):

![Formula IV](image)
In one embodiment, the compound has the formula (V):

\[
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{O}
\end{array}
\]

5 In one embodiment, the compound has the formula (VI):

\[
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{O}
\end{array}
\]

In one embodiment, the compound has the formula (VII):

\[
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{O}
\end{array}
\]

10 In one embodiment, the compound has the formula (VIII):

\[
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{O}
\end{array}
\]

In one embodiment, the compound has the formula (IX):

\[
\begin{array}{c}
\text{HO} \\
\text{OCH}_3
\end{array}
\]

In one embodiment, the compound has the formula (X):

\[
\begin{array}{c}
\text{HO} \\
\text{OCH}_3
\end{array}
\]
In one embodiment, the compound has the formula (XI):

In one embodiment, the compound has the formula (XII):

In one embodiment, the compound has the formula (XIII):

In one embodiment, the compound has the formula (XIV):

In one embodiment, the compound has the formula (XV):
In one embodiment, the compound has the formula (XVI):

In one embodiment, the compound has the formula (XVII):

In one embodiment, the compound has the formula (XVIII):

Since the disclosed active compounds may have asymmetric carbon centers, they can be present in the form of racemate, diastereomers or mixtures thereof. Therefore, the present invention also includes all these isomers and their mixtures.

*Synthesis of Active Compounds*

The disclosed active compounds having the general formula (I) may be prepared by a process as described below.
Generally, the active compounds are synthesized via nucleophilic substitution reactions. A nucleophile and a second reactant (an electrophile) are mixed in an anhydrous solvent, and stirred at room temperature to produce the active compounds. The active compounds are extracted with an organic solvent, and the resulting organic extracts are concentrated under reduced pressure to give a crude product.

The nucleophile is an amine having a formula (Ia), or a hydrochloride or hydrobromide salt thereof having a formula (Ia') as shown below:

(Ia)

(Ia')

where R is H or CH₃, Y is N or CH, and X is Cl or Br.

Alternatively, the nucleophile is a straight chain amine having a formula (Ia"):

(Ia")

where n is 1 or 3.

The electrophile is an acid chloride (such as a nonanoyl chloride), an isocyanate or isothiocyanate, or a lactone.

The nucleophile and the electrophile are typically used in a stoichiometric ratio, but the excess of one component or the other may be advantageous.

The anhydrous solvent is N,N-dimethylformamide (DMF), dichloromethane or tetrahydrofuran.
Where the nucleophile used is a hydrochloride or hydrobromide salt of an amine having a formula (Ia'), N,N-diisopropylethylamine (DIPEA) can be added to liberate the amine group.

Where the electrophile used is a lactone, 2-hydroxypyridine is added as a reaction catalyst.

Typically, the mixture is stirred at room temperature for 6 to 24 h before being extracted with an organic solvent such as dichloromethane. The organic extract is concentrated under reduced pressure to give a crude active compound, which is then purified using silica gel column chromatography or preparative high performance liquid chromatography.

**Active Compound Salts**

In some forms, it may be desirable to formulate the active compounds in pharmaceutically or cosmetically acceptable salt form, generally to improve the solubility and bioavailability and to provide an active compound that may be capable of being assimilated readily. Preferably, the pharmaceutically or cosmetically acceptable salts are suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

The active compounds may form pharmaceutically or cosmetically acceptable salts with both organic and inorganic acids. Suitable physiologically tolerated acids for salt formation may be organic and inorganic acids, such as hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric,
succinic, ascorbic, maleic, methanesulfonic, isethionic, lactic, gluconic, glucuronic, sulfamic, benzoic, tartaric, pamoic, and the like.

The salts may be prepared by contacting a free base form with an equivalent amount of the desired acid in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions may be suitable for this purpose.

The free base forms may differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvent. Otherwise, the salts may be equivalent to their respective free base forms for purposes of the invention.

The active compounds may exist in unsolvated as well as solvated forms, including hydrated forms. Such salt forms of the active compound may be provided or mixed prior to use with a physiologically acceptable solvent such as water or ethanol.

**Therapeutic Uses of Active Compounds**

**Use as Anti-oxidative Agents**

It has been found that the active compounds of general formula (I) have potent anti-oxidant activity, and reduced or no cytotoxicity. Hence, the disclosed active compounds may be capable of stopping or preventing oxidative stress in a subject. Accordingly, the
disclosed active compounds may be envisaged as being useful for use as anti-oxidative agents in the treatment, prevention, inhibition or amelioration of one or more oxidative stress related disorders or condition, and/or conditions caused by presence of free radicals in a subject.

(a.) **Use in Medicine**

Subjects having or at risk of developing an oxidative stress related disorder include those having inflammatory disorders, autoimmune disorders such as rheumatoid arthritis, lupus and neurodegenerative disease such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS), atherosclerosis, cerebral ischemia, hepatopathy, diabetes, nervous diseases, renal diseases, hepatic cirrhosis, arthritis, retinopathy of prematurity, ocular uveitis, retinal rust disease, senile cataract, asbestos diseases, bronchial failures due to smoking, cerebral edema, pulmonary edema, foot edema, cerebral infarction, coronary artery disease, hemolytic anemia, progeria, epilepsy, Crohn's disease, Kawasaki disease, collagen disease, progressive systemic sclerosis, herpetic dermatitis, immune deficiency syndrome or the like.

Such subjects may benefit from the anti-oxidative effect of the active compounds disclosed herein, when administered in pure form or with one or more other ingredient in a pharmaceutical composition as discussed below. Hence, the active compounds may be provided as a
pharmaceutical composition in the form of a medicament as discussed below.

(b) Use in Health Supplements and Cosmetic Formulations

Another aspect of using the active compounds as anti-oxidative agents is on the preventive side. Instead of waiting for the free radicals to make a long chain of free radicals and cause oxidative damage to cells and tissues, the active compounds scavenge and destroy the initiating free radicals before oxidation is set in motion, to thereby delay the onset and progress of the aging process and prevent onset of an oxidative stress related disease.

Hence, the active compounds disclosed herein may be provided in pure form or with one or more other ingredients in a health supplement. Alternatively, the active compounds may be provided in pure form or with one or more other ingredients in a cosmetic formulation as discussed below.

Pharmaceutical Compositions

The active compounds for use as an anti-oxidative agent may be administered in pure form or in an appropriate pharmaceutical composition. In general, suitable pharmaceutical compositions may be prepared according to methods which are known to those of ordinary skill in the art. The compositions comprising the active compounds disclosed herein may include a conventional
pharmaceutical carrier or diluent, and in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Examples of suitable pharmaceutical carriers or diluents include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Other suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences (Mack Publishing Company), a standard reference text in this field, or in U.S. Pharmacopeia National Formulary, 1857-1853, (1990). Typically, the carrier(s) or diluent(s) will form from about 10% to about 99.9% by weight of the compositions.

Administration of the active compounds disclosed herein, in pure form or in an appropriate pharmaceutical composition, may be carried out via any of the acceptable modes of administration or pharmaceutically acceptable means of delivery. The modes of administration and pharmaceutically acceptable means of delivery may include oral administration or delivery in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms. The dosage forms may include tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

Oral administration of the disclosed active compounds may be effected by preparing a mixture of the disclosed active compounds with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be
compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the disclosed active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations may contain the active compounds in an amount by weight percent selected from the group consisting of about 0.1% to about 70%, about 0.5% to about 65%, about 1% to about 60%, about 2% to about 55% and about 3% to about 50%.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavorings, such as cherry or orange flavor. Any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.
In addition, the active compounds may be incorporated into sustained-release preparation and formulations. The active compounds disclosed herein may be administered parenterally or intraperitoneally. Solutions of the disclosed active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use may include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms may be brought about by various antibacterial and antifungal agents, for example,
parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. Prolonged absorption of the injectable compositions can also be brought about by including in the composition an agent which delays absorption, for example, aluminium monostearate and gelatin.

Preferably, the pharmaceutical form may further include a suitable buffer to minimise acid hydrolysis. Suitable buffer agents are well known to those skilled in the art and include, but are not limited to, phosphates, citrates, carbonates and mixtures thereof.

The active compounds may also be administered in the form of a "prodrug". A prodrug is an inactive form of a compound which is transformed in vivo to the active form. Suitable prodrugs include esters, phosphonate esters etc, of the active form of the compound.

The active compounds in pharmaceutically acceptable form may be administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compounds employed; the metabolic stability and length of action of the compounds; the age, body weight, general health, sex and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease states; and the patient undergoing treatment.

Single or multiple administrations of the pharmaceutical compositions according to the invention may be carried out. One skilled in the art would be able, by routine experimentation, to determine effective, non-toxic dosage levels of the compound and/or composition of the invention and an administration regime which would be
suitable for treating the diseases and/or conditions to which the compounds and compositions are applicable.

It will be apparent to one of ordinary skill in the art that the optimal course of treatment, such as the number of doses of the compound or composition of the invention given per day for a defined number of days, can be ascertained using conventional course of treatment determination tests.

Generally, an effective dosage per 24 hours for use of the active compounds as anti-oxidative agents in a pharmaceutical composition may be in the range of about 0.5 mg per kg body weight to about 10 mg per kg body weight; suitably, about 1 mg per kg body weight to about 6 mg per kg body weight. Alternatively, an effective dosage may be up to about 20 mg per kg body weight. For example, generally, an effective dosage is expected to be in the range of about 10 to about 20 mg per kg body weight.

The active compounds of the invention may be used in combination with other known treatments or anti-oxidative agents. Combinations of active agents, including the active compounds of the invention, may be synergistic.

**Cosmetic Formulations**

The active compounds disclosed herein may also be used to provide anti-oxidative effect in the form of cosmetic formulations such as anti-aging creams, lipstick, face cream, body lotion, moisture creams, burn remedies containing local anesthetics and the like. The active compounds have protective effect against damage to
the skin that is induced by UV light, and hence prevent damage caused by radiation from natural or artificial sources such as the sun, either alone or in combination with sunscreen agents such as PABA.

The active compounds may be used individually or in combination with one or more other ingredients in the cosmetic formulation, such as solvents, emollients, humectants, emulsifiers, surfactants, thickeners, coloring agents, preservatives (such as anti-bacterial agents, anti-viral agents, anti-fungal agents), vitamins, antibiotics, anti-inflammatory agents, anti-acne agents, anti-irritants, anti-dandruff agents, anti-perspirants, anti-wrinkle agents, whitening agents, moisturizing agents, and fragrances, among others. Cosmetically acceptable ingredients and formulations are also discussed in, for example, FDA Cosmetics Handbook, U.S. Food and Drug Administration; Handbook of Cosmetic and Personal Care Additives, Ash and Ash, compilers, 1994, Chemical Publishing, New York, N.Y.; and Remington's Pharmaceutical Sciences, 18.sup.th ed., Gennaro, ed., 1990, Mack Publishing.

The active compounds are "cosmetically acceptable" in terms of being compatible with the other ingredients of the cosmetic formulation, and not deleterious to the recipient thereof.

The cosmetic formulations to which the active compounds may be added are preferably in a form suitable for topical administration, although cosmetic preparations in a form suitable for administration by parenteral injection (such as subcutaneous, intramuscular or intravenous injection), oral ingestion (such as
capsules, tablets, caplets and elixirs), or inhalation (such as by intranasal inhalation or oral inhalation) are also envisaged. Topical formulations, preferably hypoallergenic and pH-controlled, include liquid or semi-liquid preparations such as lotions or liniments, creams, ointments or pastes, drops, tinctures, salves, patches, powders and solutions containing the active compounds disclosed herein and one or more cosmetically acceptable carriers, and optionally any other ingredients as discussed above.

Methods for preparing topical, injectable, oral and aerosol compositions comprising the active compounds disclosed herein and other ingredients described above are apparent to those skilled in the art, and are described in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa.

The dosage, frequency and duration of administration of a cosmetic formulation comprising the disclosed active compounds is dependent on factors including the nature of the formulation (for example, its concentration, the presence or lack of other active ingredients, and the delivery system used), the severity and extent of the condition being treated, the form, route and site of administration, the discretion of the individual being treated, and in some cases, the judgment of a skin care professional (for example, a dermatologist or a cosmetologist). The dosage, frequency and duration required to achieve a cosmetic effect can be readily determined by one of ordinary skill in the art.

Typical effective dosages are expected to be in the range of about 0.01 µg/mL to about 2 mg/mL. Typically,
the active compounds are used in an amount of about 0.01 µg/mL to about 1.5 mg/mL, about 0.01 µg/mL to about 1 mg/mL, about 0.01 µg/mL to about 100 µg/mL, about 0.01 µg/mL to about 1 µg/mL, about 0.1 µg/mL to about 2 mg/mL, about 1 µg/mL to about 2 mg/mL, about 10 µg/mL to about 2 mg/mL, about 100 µg/mL to about 2 mg/mL, about 1 mg/mL to about 2 mg/mL or about 1.5 mg/mL to about 2 mg/mL.

Typical frequencies of administration are expected to be about once, twice, three times, four times, five times, or six times per week, or about once, twice, three times, four times, five times, or six times per day. In some embodiments, the administration is carried out about once to about three times per day. In some embodiments, the administration is carried out about twice to about four times per day. In some embodiments, the administration is carried out more than about three times per day. Where administration is carried out twice per day, the administration is typically in the morning and in the evening.

Non-therapeutic Uses of Active Compounds

Food, cosmetic and personal care products are susceptible to oxidative damage, which can adversely affect the flavour, odour and colour of the product, making them less appealing to consume or use. Antioxidants can stabilize such products against oxidation and thereby improve their quality and storage potential.
Use as Stabilizers in Food

The most common molecules attacked by oxidation are unsaturated fats. Oxidation causes unsaturated fats to turn rancid, resulting in discolorization and development of unpleasant tastes. Hence, it is important to avoid oxidation in oil- and fat-rich foods. The term "food" and "food product" as used herein refers to any edible substance for human consumption as well as feed for animal consumption (e.g. pet food, animal feed). Accordingly, edible substances suitable for human or animal consumption that may be stabilized against oxidation using the active compounds disclosed herein include, but are not limited to, frying oils and fats such as tallow, lard, peanut oil, corn oil, cottonseed oil, olive oil, safflower oil, soybean oil, coconut oil, shortening, cooking oils, salad oils and dressings; potato flakes; bakery products; meat emulsions; precooked cereals; instant noodles; soybean milk; chicken products; emulsion products such as sausage; mayonnaise and margarine; frozen fish; frozen pizza; cheese and animal foods. The oils and fats may be naturally-occurring, such as animal or vegetable fats, or synthetic materials.

The active compounds disclosed herein may be used in an amount based on the weight of the edible substance, which amount is effective as an anti-oxidant, that is an amount sufficient to stabilize, or retard the deterioration of, the edible substances to be stored and used to prepare foods in a normal and acceptable manner. Typically, the amount of the active compound employed is any amount which may have a significant stabilizing
effect, and may depend on various factors, such as the desired period of stability of the edible substance, the rate of deterioration of the edible substance, the type of oxidation to be stabilized against, and the type of edible substance etc. For example, when a prolonged storage life of the edible substance before use is desired, increased amounts of the active compounds may be used. Typically, the active compounds are used in an amount of about 0.001% to about 5%, of about 0.005% to about 5%, of about 0.01% to about 5%, of about 0.05% to about 5%, of about 0.1% to about 5%, of about 0.5% to about 5%, of about 1% to about 5%, of about 2% to about 5%, of about 3% to about 5%, of about 4% to about 5%%, of about 0.001% to about 4%, of about 0.001% to about 3%, of about 0.001% to about 2%, or of about 0.001% to about 1%, by weight based on the weight of the edible substance.

The active compounds disclosed herein may be used in pure form or in combination with one or more other antioxidants to achieve desirable combinations of properties of stability. For example, the active compounds disclosed herein may be used in combination with one or more of the phenolics (e.g. BHA and BHT); tocopherols (e.g. α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol and mixtures thereof); benzylphosphonates (e.g. dimethyl-2, 5-di-tert-butyl-4-hydroxybenzylphosphonate and diethyl-3, 5-di-tert-butyl-4-hydroxybenzylphosphonate); esters of (3, 5-di-tert-butyl-4-hydroxyphenyl) propionic acid, (5-tert-butyl-4-hydroxy-3-methylphenyl) propionic acid, (3, 5-dicyclohexyl-4-hydroxyphenyl) propionic acid or 3, 5-di-tert-butyl-4-hydroxyphenyl acetic acid with mono- or polyhydric
alcohols; ascorbic acid (vitamin C); phosphites and phosphonites (e.g. triphenyl phosphite, diphenyl alkyl phosphites, phenyl dialkyl phosphites etc.); and rosemary extract, among others.

The active compounds may also be used in combination with one or more other food additives such as emulsifiers (e.g. mono- and di-glycerides of saturated or unsaturated fatty acids such as monoglyceryl palmitate, polyoxyethylene derivatives of hexahydric alcohols such as sorbitol, glycols, glycol esters, polyglycerol esters, sorbitan esters, stearoyl lactylate, acetic acid esters, lactic acid esters, citric acid esters, acetylated monoglyceride, diacetyl tartaric acid esters, polyoxyethylene sorbitan esters such as polysorbate 80, sucrose esters, lecithin, egg yolk, and mixtures thereof), suspension agents and colorings to provide the desired qualities in the final food product.

Preferably, the presence of the active compounds disclosed herein does not materially affect the manner in which the edible substance is formulated or in which it is used to prepare food or food products. The active compounds may be added at the time of food preparation or may be premixed with the edible fat or fatty oils to stabilize them prior to food preparation. Preferably, the active compounds are uniformly admixed in the edible substance. The active compounds disclosed herein are suitable for use in both small-scale and large-scale production of food and food products.
(B) Use as Stabilizers in Cosmetic and Personal Care Products

The active compounds disclosed herein are also suitable for stabilizing cosmetic and personal care products, particularly fat-based cosmetic and personal care products, against oxidative damage that can cause rancidity and product discoloration. Cosmetic and personal care products that may be stabilized by the active compounds include those that may be applied to any part of the human body, such as skin, hair or nails. Exemplary cosmetic and personal care products include, but are not limited to, lipsticks and other lip care products, make-up, foundations, facial masks, detergents, hair colorants, liquid soaps, bar soaps, creams, lotions, bath gels, hand cleaners, facial cleansers, exfoliants, sunscreens, conditioners, shampoos, shaving creams, hair detanglers, hot oil treatments, toilet waters, and fabric softeners, and the like.

Typically, the amount of the active compound employed is any amount which may have a significant stabilizing effect, and may depend on various factors, such as the desired period of stability of the cosmetic or personal care product, the rate of deterioration of the cosmetic or personal care product, the type of oxidation to be stabilized against, and the type of the cosmetic or personal care product. Typically, the active compounds are used in an amount of about 0.001% to about 5%, of about 0.005% to about 5%, of about 0.01% to about 5%, of about 0.05% to about 5%, of about 0.1% to about 5%, of about 0.5% to about 5%, of about 1% to about 5%,
of about 2% to about 5%, of about 3% to about 5%, of
about 4% to about 5%, of about 0.001% to about 4%, of
about 0.001% to about 3%, of about 0.001% to about 2%, or
of about 0.001% to about 1%, by weight based on the
weight of the cosmetic or personal care product.

The active compounds may be used in pure form or in
combination with one or more other ingredients in the
cosmetic and personal care product, such as solvents,
emollients, humectants, emulsifiers, surfactants,
thickeners, coloring agents, preservatives (such as anti-
bacterial agents, anti-viral agents, anti-fungal agents),
vitamins, antibiotics, anti-inflammatory agents, anti-
acne agents, anti-irritants, anti-dandruff agents, anti-
perspirants, anti-wrinkle agents, whitening agents,
moisturizing agents, and fragrances, among others.

Suitable ingredients and formulations are also discussed
in, for example, FDA Cosmetics Handbook, U.S. Food and
Drug Administration; Handbook of Cosmetic and Personal
Care Additives, Ash and Ash, compilers, 1994, Chemical
Publishing, New York, N.Y.; and Remington's
Pharmaceutical Sciences, 18th ed., Gennaro, ed.,
1990, Mack Publishing. Methods for preparing topical,
injectable, oral and aerosol compositions suitable for
use in cosmetic and personal care products comprising the
active compounds disclosed herein and other ingredients
described above are apparent to those skilled in the art,
and are described in, for example, Remington's
Company, Easton, Pa.

One skilled in the art will recognize in light of
the present disclosure that although the specified
materials and conditions are important in practicing the invention, unspecified materials and conditions are not excluded as long as they do not prevent the benefits of the invention from being realized.

5

**Brief Description of Drawings**

The accompanying drawings illustrate a disclosed embodiment and serves to explain the principles of the disclosed embodiment. It is to be understood, however, that the drawings are designed for purposes of illustration only, and not as a definition of the limits of the invention.

Fig. 1 shows the dose response curve of analogue JC017 in cytotoxicity assays using A549 and HepG2 cell lines.

Fig. 2 shows the dose response curve of analogue JC058 in cytotoxicity assays using A549 and HepG2 cell lines.

Fig. 3 shows a comparison of the cytotoxicity of analogues JC017 and JC058 in a cytotoxicity assay using the A549 cell line.

Fig. 4 shows a comparison of the cytotoxicity of analogues JC017 and JC058 in a cytotoxicity assay using the HepG2 cell line.

**Examples**

Non-limiting embodiments of the disclosed active compounds will be further described in greater detail by
reference to specific Examples, which should not be construed as in any way limiting the scope of the invention.

5 Synthesis of Capsaicin Analogues

Materials

The chemical reagents and solvents used in the following examples were purchased from Sigma-Aldrich and Merck.

Analytical Protocols

(a) Analytical High Performance Liquid Chromatography (HPLC)

Analytical HPLC was performed on a Waters HPLC system equipped with a Waters 2998 PDA detector, Waters 2695 separation module using a Phenomenex Luna C18(2) (4.6 mm i.d. × 150 mm, 5µ) column. A gradient elution starting with 20% CH₃CN, 80% (0.1% formic acid/H₂O), and ending with 100% CH₃CN at a flow rate of 1.0 mL/min over 15 min was used.

(b) Preparative HPLC

Preparative HPLC was performed on a Shimadzu LC-8A HPLC system equipped with a CBM-20A PDA detector, Gilson 215 liquid handler and fraction collector using a X-Bridge Prep cis (30 mm i.d. × 50 mm, 5µ) column. An isocratic elution with 20% CH₃CN, 80% (0.1% formic acid/H₂O) at a flow rate of 20.0 mL/min for 5 min was used. This was followed by a gradient elution starting
with 20% CH$_3$CN, 80% (0.1% formic acid/H$_2$O), and ending with 100% CH$_3$CN at a flow rate of 20.0 mL/min over 45 min.

(c) **Liquid Chromatography-Mass Spectrometry (LC-MS)**

LC-MS data was collected on a Shimadzu LCMS-IT-TOF instrument equipped with SPD-M20A PDA detector, LCMS-IT-TOF MS detector and LC-20AD binary gradient pump using a Shimpack VP-ODS (2.0 mm i.d. × 150 mm) column. An isocratic elution with 20% H$_2$O and 80% CH$_3$CN at a flow rate of 0.2 mL/min over 3 min was used.

**Example 1: Synthetic Procedure for Analogues JC004, JC005 and JCOI1**

To a solution of the hydrochloride or hydrobromide salt of an amine (1 mmol) in anhydrous N,N-dimethylformamide (DMF) (2 mL) was added N,N-diisopropylethylamine (DIPEA) (2 mmol) to liberate the amine. After stirring at room temperature for 10 min, nonanoyl chloride (1 mmol) was added. The solution was stirred at room temperature for 6 to 24 h. After the reaction, water (40 mL) was added to the solution. The reaction mixture was transferred to a separating funnel and extracted with dichloromethane, CH$_2$Cl$_2$ (3 × 6 mL). The organic extracts were concentrated under reduced pressure.
to give a crude product. The crude product was then purified by silica gel column chromatography (using hexane/ethyl acetate, 2:1 v/v, as eluent) or preparative HPLC (using the protocol set out in "Analytical Protocols" above) to give the final product.

**Example 2: Synthetic Procedure for Analogues JCO01, JC008 and JC013**

![Chemical Structure](image)

To a solution of amine (1 mmol) in anhydrous dichloromethane or N,N-dimethylformamide (DMF) (2 mL) were added _N,N-diisopropylethylamine (DIPEA) (1 mmol) and nonanoyl chloride (1 mmol). The solution was stirred at room temperature for 6 to 24 h. After the reaction, water (20 mL) was added to the solution. The reaction mixture was transferred to a separating funnel and extracted with dichloromethane, CH2Cl2 (3 × 10 mL). The organic extracts were concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (using hexane/ethyl acetate, 2:1 v/v, as eluent) or preparative HPLC (using the protocol set out in "Analytical Protocols" above) to give the final product.
**Example 3**: Synthetic Procedure for Analogues JC006, JC007, JC010, JC014, JC015, JC017 and JC058

To a solution of the hydrochloride or hydrobromide salt of an amine $(1-2$ mmol) in anhydrous dichloromethane, tetrahydrofuran or $N,N$-dimethylformamide (DMF) $(2-4$ mL) was added $N,N$-diisopropylethylamine (DIPEA) $(1-2$ mmol) to liberate the amine. After stirring at room temperature for 10 min, isocyanate or isothiocyanate $(1-2$ mmol) was added. The solution was stirred at room temperature for 6 to 24 h. After the reaction, water $(20$ mL) was added to the solution. The reaction mixture was transferred to a separating funnel and extracted with dichloromethane, CH$_2$Cl$_2$ $(3 \times 10$ mL). The organic extracts were concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (using hexane/ethyl acetate, 2:1 v/v, as eluent) or preparative HPLC (using the protocol set out in "Analytical Protocols" above) to give the final product.

For analogues that precipitated during the extraction process with dichloromethane, the suspension containing the precipitated analogues was transferred to a Falcon tube and centrifuged. The supernatant was discarded. The pellet was re-suspended with ethyl acetate $(5$ mL) and centrifuged. The re-suspension and centrifugation steps were carried out twice. The crude product obtained was further purified by preparative HPLC.
Example 4: Synthetic Procedure for Analogues JC003, JC009, JC012, JC016 and JC018–JC022

To a solution of an amine (1–2 mmol) in anhydrous dichloromethane, tetrahydrofuran or N,N-dimethylformamide (DMF) (2–4 mL) was added isocyanate or isothiocyanate (1–2 mmol). The solution was stirred at room temperature for 6 to 24 h. After the reaction, water (20 mL) was added to the solution. The reaction mixture was transferred to a separating funnel and extracted with dichloromethane, CH$_2$Cl$_2$ (3 × 10 mL). The solvent extracts were concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (using hexane/ethyl acetate, 2:1 v/v, as eluent) or preparative HPLC (using the protocol set out in "Analytical Protocols" above) to give the final product.

For analogues that precipitated during the extraction with dichloromethane, the suspension containing the precipitated analogues was transferred to a Falcon tube and centrifuged. The supernatant was discarded. The pellet was re-suspended with ethyl acetate (5 mL) and centrifuged. The re-suspension and centrifugation steps were carried out twice. The crude product obtained was further purified by preparative HPLC.
Example 5: Synthetic Procedure for Analogues JC023-JC026

To a solution of lactone (2 mmol) and 2-hydroxypyridine (0.2 mmol) in anhydrous dichloromethane (5 mL) was added an amine (2.2 mmol). The mixture was stirred at room temperature for 6 to 24 h. After the reaction, water (20 mL) was added. The reaction mixture was transferred to a separating funnel and extracted with dichloromethane, \( \text{CH}_2\text{Cl}_2 \) (3 × 10 mL). The solvent extracts were concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (using hexane/ethyl acetate, 1:1 v/v as eluent) or preparative HPLC (using the protocol set out in "Analytical Protocols" above) to give the final product.

Example 6: Analytical Data on Capsaicin Analogues

The capsaicin analogues prepared in Examples 1-5 above were analyzed using the analytical protocols set out above. The resulting mass spectral, yield and purity data for each analogue are tabulated in Table 1 below.
Table 1. Analytical Data on Capsaicin Analogues

<table>
<thead>
<tr>
<th>Test Sample</th>
<th>Structure</th>
<th>Exact Mass (calculated)</th>
<th>Exact Mass (observed)</th>
<th>Purified Yield (%)</th>
<th>HPLC Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JC001</td>
<td><img src="image1" alt="Structure" /></td>
<td>292.1907 [M+H]^+</td>
<td>292.1863 [M+H]^+</td>
<td>87.0</td>
<td>&gt;99</td>
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<tr>
<td>JC003</td>
<td><img src="image2" alt="Structure" /></td>
<td>307.2022 [M+H]^+</td>
<td>307.2023 [M+H]^+</td>
<td>60.0</td>
<td>99</td>
</tr>
<tr>
<td>JC004</td>
<td><img src="image3" alt="Structure" /></td>
<td>294.2069 [M+H]^+</td>
<td>294.2061 [M+H]^+</td>
<td>88.6</td>
<td>98</td>
</tr>
<tr>
<td>JC005</td>
<td><img src="image4" alt="Structure" /></td>
<td>294.2069 [M+H]^+</td>
<td>294.2055 [M+H]^+</td>
<td>81.5</td>
<td>98</td>
</tr>
<tr>
<td>JC006</td>
<td><img src="image5" alt="Structure" /></td>
<td>309.2178 [M+H]^+</td>
<td>309.2171 [M+H]^+</td>
<td>39.0</td>
<td>98</td>
</tr>
<tr>
<td>JC007</td>
<td><img src="image6" alt="Structure" /></td>
<td>309.2178 [M+H]^+</td>
<td>309.2170 [M+H]^+</td>
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<td>98</td>
</tr>
<tr>
<td>JC008</td>
<td><img src="image7" alt="Structure" /></td>
<td>249.1967 [M+H]^+</td>
<td>249.1965 [M+H]^+</td>
<td>92.0</td>
<td>96</td>
</tr>
<tr>
<td>JC009</td>
<td><img src="image8" alt="Structure" /></td>
<td>264.2076 [M+H]^+</td>
<td>264.2080 [M+H]^+</td>
<td>75.0</td>
<td>&gt;99</td>
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<tr>
<td>JC010</td>
<td>[\text{295.2022} [\text{M+H}]^+]</td>
<td>[\text{295.2011} [\text{M+H}]^+]</td>
<td>9.8</td>
<td>&gt;99</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>JC011</td>
<td>[\text{280.1913} [\text{M+H}]^+]</td>
<td>[\text{280.1905} [\text{M+H}]^+]</td>
<td>30.3</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC012</td>
<td>[\text{279.2073} [\text{M+H}]^+]</td>
<td>[\text{279.2064} [\text{M+H}]^+]</td>
<td>20.9</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>JC013</td>
<td>[\text{264.1964} [\text{M+H}]^+]</td>
<td>[\text{264.1957} [\text{M+H}]^+]</td>
<td>68.5</td>
<td>&gt;99</td>
<td></td>
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<tr>
<td>JC014</td>
<td>[\text{281.1865} [\text{M+H}]^+]</td>
<td>[\text{281.1860} [\text{M+H}]^+]</td>
<td>17.6</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>JC015</td>
<td>[\text{281.1865} [\text{M+H}]^+]</td>
<td>[\text{281.1859} [\text{M+H}]^+]</td>
<td>18.3</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC016</td>
<td>[\text{251.1760} [\text{M+H}]^+]</td>
<td>[\text{251.1750} [\text{M+H}]^+]</td>
<td>9.4</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>JC017</td>
<td>[\text{267.1709} [\text{M+H}]^+]</td>
<td>[\text{267.1704} [\text{M+H}]^+]</td>
<td>2.6</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC018</td>
<td>[\text{297.1637} [\text{M+H}]^+]</td>
<td>[\text{297.1635} [\text{M+H}]^+]</td>
<td>12.3</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC019</td>
<td>295.1480 ([\text{M+H}]^*)</td>
<td>295.1476 ([\text{M+H}]^*)</td>
<td>45.1</td>
<td>&gt;99</td>
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<tr>
<td>JC020</td>
<td>236.1763 ([\text{M+H}]^*)</td>
<td>236.1756 ([\text{M+H}]^*)</td>
<td>45.7</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC021</td>
<td>252.1534 ([\text{M+H}]^*)</td>
<td>252.1525 ([\text{M+H}]^*)</td>
<td>81.7</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC022</td>
<td>267.1531 ([\text{M+H}]^*)</td>
<td>267.1521 ([\text{M+H}]^*)</td>
<td>84.7</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC023</td>
<td>236.1645 ([\text{M+H}]^*)</td>
<td>236.1651 ([\text{M+H}]^*)</td>
<td>92.6</td>
<td>&gt;99</td>
<td></td>
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<tr>
<td>JC024</td>
<td>264.1964 ([\text{M+H}]^*)</td>
<td>264.1962 ([\text{M+H}]^*)</td>
<td>39.2</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC025</td>
<td>252.1600 ([\text{M+H}]^*)</td>
<td>252.1594 ([\text{M+H}]^*)</td>
<td>49.4</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>JC026</td>
<td>280.1913 ([\text{M+H}]^*)</td>
<td>280.1901 ([\text{M+H}]^*)</td>
<td>22.0</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>
Anti-oxidant Activity and Cytotoxicity
of Capsaicin Analogues

Total anti-oxidant activity can be measured using various assays that are based on different reaction mechanisms. These include the Oxygen Radical Absorbance Capacity (ORAC) assay, the Total Radical Trapping Anti-oxidant Parameter (TRAP) assay, the Total Equivalent Anti-oxidant Capacity (TEAC) assay, and the 2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Capacity (DPPH) assay. On the basis of chemical principles, the ORAC assay is closely related to the biological functions of chain-breaking anti-oxidants and has been used extensively in anti-oxidant studies. Hence, the ORAC assay was used to test the anti-oxidant activities of the capsaicin analogues prepared in Example 1-5 above.

The DPPH assay is also a simple and accurate method for measuring anti-oxidant levels. The DPPH assay was used as a comparison to the ORAC assay for obtaining additional information on the reducing power of the test samples (Mahattanatawee et al., 2006, J. Agric. Food Chem. 54, 7355-7363).

Materials

2,2'-azobis (2-methylpropionamide) dihydrochloride (AAPH), 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and resazurin were purchased from Sigma-Aldrich. Fluorescence natrium was purchased from Merck and Trolox was purchased from Acros. All measurements were carried out with Tecan Infinite 200.
**ORAC Assay**

The ORAC assay is based on the free radical damage caused to a fluorescent probe. In general, the assay applies a thermal peroxyl radical (R00") generator, the azo compound 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH), to give a steady flux of peroxyl radicals in an air-saturated solution. The loss of fluorescence intensity of a fluorescein probe is an indication of the extent of the damage resulting from its reaction with the peroxyl radical. The protective effect of an anti-oxidant is measured by assessing the area under the fluorescence decay curve (AUC) of the sample as compared to that of the blank in which no anti-oxidant is present (Ou et al., 2001, J. Agric. Food Chem. 49, 4619-4626).

The ORAC assay was performed as described by Huang et al (Huang et al., 2002. J. Agric. Food Chem. 50, 4437-4444) with some minor modifications. Firstly, the capsaicin analogues were dissolved in methanol and added in volumes of 10 µl/well into a black 96-well plate in duplicate or triplicate with serial dilutions. 150 µl of 80 nM fluorescein was then added to the 96-well plate, followed by the addition of 40 µl of 100 mM AAPH (2,2'-azobis (2-amidinopropane) dihydrochloride). The plate was read immediately after addition of the AAPH at two minute intervals at an excitation wavelength of 485 nM and an emission wavelength of 535 nM at 37°C for 2 hours.

The template of a 96-well plate in an ORAC assay is as follows:
In wells A1-H9, 10 µl/well of the test sample, 150 µl/well of 80 nM fluorescein and 40 µl/well 100 mM AAPH were added.

In wells A10-H11, a Trolox serial dilution was prepared with methanol starting at a final assay concentration of 100 µM. The concentrations in the serial dilution were 100 µM, 50 µM, 25 µM, 12.5 µM, 6.25 µM, 3.125 µM, 1.563 µM and 0.781 µM. A series of 10 µl/well of Trolox, 150 µl 80 nM fluorescein and 40 µl/well 100 mM AAPH were prepared in duplicate.

In wells A12-H12, methanol 10 µl/well, 150 µl/well 80 nM fluorescein and 40 µl/well 100 mM AAPH were added to provide the Blank reading.

**Data Processing:**

The ORAC values were calculated according to Huang et al. (supra). The net area under the curve (AUC) of the Trolox standard and the test samples were also calculated using the following equation:

\[
AUC = 0.5 + (R2/R1) + (R3/R1) + (R4/R1) + \ldots + 0.5(Rn/R1) \quad (Eq. 1)
\]
where \( R_l \) is the fluorescence reading at the initiation of the reaction and \( R_n \) is the final measurement.

The Net AUC was calculated using the following equation:

\[
\text{Net AUC} = \text{AUC}_{\text{sample}} - \text{AUC}_{\text{blank}} \quad (\text{Eq. 2.})
\]

When net AUC values were calculated from these kinetic curves and plotted against Trolox concentration, a linear relationship was observed. The standard curve was interpolated to determine the readings of the unknown test samples. The relative Trolox equivalent ORAC value is expressed as \( \mu \text{mol TE} / \mu \text{mol capsaicin analogue} \). A higher Trolox equivalent value would imply a higher antioxidant activity.

**DPPH Assay**

DPPH is one of a few stable and commercially available organic nitrogen radicals and has an absorption maximum at 517 nm. The ability of a compound to scavenge stable \([\text{DPPH}]^-\) is a widely used method for evaluating Radical-Scavenging Capacity (RSC) in a relatively short time compared to other methods. Upon reduction, the colour of the solution fades as illustrated by the following chemical reaction:
The progress of the reaction is easily monitored by a spectrophotometer (Molyneux, 2004; Eklund et al., 2005; and Shama et al., 2009). The DPPH assay was modified and carried out with a 9β-well plate (Molyneux, 2004; Eklund et al., 2005; Shama et al., 2009). A 190 µl/well DPPH solution (150 µM) in methanol was mixed with a 10 µl/well sample dissolved in methanol. The progress of the reaction was monitored by determining the absorbance of the mixture at 517 nm after 30 min.

The template of a 96-well plate in a DPPH assay is as follows:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>S</td>
<td>S</td>
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<td>S</td>
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<td>S</td>
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<td>S</td>
<td>Negative control</td>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>Negative control</td>
<td>Blank</td>
</tr>
</tbody>
</table>
In wells Al-H10, 10 µl/well test sample in methanol and 190 µl/well 150 µM DPPH were added. In wells Al-H11, 10 µl/well methanol and 190 µl/well 150 µM DPPH were added as negative controls. In wells A12-H12, 200 µl/well methanol were added to provide the Blank reading.

Data Processing:

The percentage of the DPPH scavenging activity was calculated as based on the following equation:

\[
\% \text{ activity} = \left( \frac{(\text{Sample}_{\text{OD}_{517\text{nm}}} - \text{Blank}_{\text{OD}_{517\text{nm}}})}{(\text{Negative Control}_{\text{OD}_{517\text{nm}}} - \text{Blank}_{\text{OD}_{517\text{nm}}})} \right) \times 100
\]

(Eq. 3)

The percentage of the remaining [DPPH]* is proportional to the anti-oxidant concentration, and the concentration that scavenges 50% of the initial [DPPH]* is defined as EC50.

Cytotoxicity Assay

The cytotoxicity assay was conducted using the HepG2 (human hepatocellular carcinoma, ATCC HB-8065) and A549 (human lung carcinoma, ATCC CCL-185) cell lines. The assay is based on the use of an indicator dye resazurin to measure the metabolic capacity of a cell. A viable cell would retain the ability to reduce resazurin to resorufin, which is a highly fluorescent compound.
Conversely, a non-viable cell would rapidly lose its metabolic capacity, and hence would not reduce the resazurin to generate the fluorescent resorufin signal.

100 µL of 10VmL HepG2 or A549 cells was added to each well in a 96-well plate. The cells were incubated at 37°C overnight. On the second day, 10 µL of the test sample was then added to each well and the mixture incubated for 24 h at 37°C. On the third day, 20 µL of 1.8 mg/mL resazurin were added to each well and the mixture incubated for 4 h at 37°C. The plate was then read at an excitation wavelength of 535 nm and an emission wavelength of 590 nm with a Tecan Infinite 200 microplate reader.

The template of the 9β-well plate used in a cytotoxicity assay was similar to the template used in the DPPH assay, except that 10% DMSO was used as the solvent for the test sample and controls. The data was also processed using the same equation as in the DPPH assay (i.e. Eq. 3).

**Example 7: Anti-oxidant Activity of Capsaicin Analogues**

The anti-oxidant activities of the various capsaicin analogues prepared in Examples 1-5 above were determined using the ORAC and DPPH assays. The anti-oxidant activities of the various analogues are shown in Table 2 below.
Table 2. Anti-oxidant Activities of Capsaicin Analogues

<table>
<thead>
<tr>
<th>Test Sample</th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
<th>ORAC (μmol TE/μmol)</th>
<th>DPPH EC50 (μM)</th>
<th>Cytotoxicity in HepG2 IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin</td>
<td><img src="image" alt="capsaicin Structure" /></td>
<td>C_{18}H_{27}NO_{3}</td>
<td>305.41</td>
<td>3.3</td>
<td>69</td>
<td>1/8</td>
</tr>
<tr>
<td>JC001</td>
<td><img src="image" alt="JC001 Structure" /></td>
<td>C_{17}H_{22}NO_{3}</td>
<td>291.4</td>
<td>NA</td>
<td>&gt;340</td>
<td>&gt;350</td>
</tr>
<tr>
<td>JC003</td>
<td><img src="image" alt="JC003 Structure" /></td>
<td>C_{17}H_{26}N_{2}O_{3}</td>
<td>306.4</td>
<td>NA</td>
<td>&gt;320</td>
<td>&gt;350</td>
</tr>
<tr>
<td>JC004</td>
<td><img src="image" alt="JC004 Structure" /></td>
<td>C_{17}H_{27}NO_{3}</td>
<td>293.4</td>
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<td>108</td>
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<td><img src="image" alt="JC005 Structure" /></td>
<td>C_{17}H_{27}NO_{3}</td>
<td>293.4</td>
<td>2.2</td>
<td>77</td>
<td>&gt;350</td>
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<td>C_{17}H_{28}N_{2}O_{3}</td>
<td>308.4</td>
<td>1.5</td>
<td>93</td>
<td>&gt;350</td>
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<td>C_{17}H_{29}N_{2}O_{3}</td>
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<td>1.6</td>
<td>178</td>
<td>&gt;350</td>
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<td>C_{15}H_{24}N_{2}O</td>
<td>248.36</td>
<td>NA</td>
<td>&gt;400</td>
<td>&gt;350</td>
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</table>
| JC009 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_15\text{H}_{25}\text{N}_3\text{O}
\end{array}
\] | 263.38 | 0.04 | >380 | >350 |
|------|---------------------------------|--------|------|-------|-------|
| JC010 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_16\text{H}_{26}\text{N}_2\text{O}_2
\end{array}
\] | 294.39 | 2.5 | 59   | >350  |
| JC011 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_16\text{H}_{23}\text{NO}_3
\end{array}
\] | 279.37 | 2.1 | 36   | >350  |
| JC012 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_16\text{H}_{26}\text{N}_2\text{O}_2
\end{array}
\] | 278.39 | 1.3 | >350 >350 |
| JC013 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_16\text{H}_{25}\text{NO}_2
\end{array}
\] | 263.38 | 0.2 | >380 >350 |
| JC014 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3
\end{array}
\] | 280.18 | 3.4 | 89   | >350  |
| JC015 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3
\end{array}
\] | 280.18 | 0.5 | >350 >350 |
| JC016 | \[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2
\end{array}
\] | 250.17 | 3.9 | >400 >350 |
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<th>JC017</th>
<th>C_{14}H_{22}N_{2}O_{3}</th>
<th>266.16</th>
<th>6.3</th>
<th>40</th>
<th>&gt;350</th>
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<td>0.2</td>
<td>&gt;340</td>
<td>&gt;350</td>
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<td>NA</td>
<td>&gt;420</td>
<td>&gt;350</td>
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<td>251.15</td>
<td>0.6</td>
<td>&gt;390</td>
<td>&gt;350</td>
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<td>JC022</td>
<td>C_{14}H_{22}N_{2}OS</td>
<td>266.15</td>
<td>3.8</td>
<td>&gt;376</td>
<td>&gt;350</td>
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<td>&gt;350</td>
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<td>251.15</td>
<td>2.2</td>
<td>28</td>
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Comparative Examples

Comparative Example 1

Comparison of Anti-oxidant Activity of Capsaicin Analogues and Capsaicin

Capsaicin analogues with differing levels of anti-oxidant activity were prepared and analyzed as set out in Examples 1-7 above.

From Table 2, it can be seen that, of all the analogues, the analogue JC017 demonstrated the most potent anti-oxidant activity. The anti-oxidant activity of JC017 was 6.3 µmol TE/µmol in the ORAC assay and the EC50 was 40 µM in the DPPH. In comparison, the anti-oxidant activity of capsaicin was about 3.3 µmol TE/µmol in the ORAC assay and the EC50 was 69 µM in the DPPH assay.

Analogues JC014, JC016, JC018, JC022 and JC026 exhibited similar antioxidant activities to capsaicin in the ORAC assay. The activities of these analogues in the ORAC assay ranged from 3.4 µmol TE/µmol to 3.9 µmol TE/µmol. In the DPPH assay, the EC50 of analogues JC014, JC018 and JC026 ranged from 30 µM to 89 µM, which is similar to the EC50 of capsaicin. However, analogues JC016 and JC022 did not exhibit any nitrogen radical-scavenging activity in the DPPH assay.
The analogues JC004, JC005, JC006, JC007, JC010, JC011, JC012, JC023, JC024 and JC025 showed moderate activity ranging from 1.3 µmol TE/µmol to 2.5 µmol TE/µmol in the ORAC assay. In the DPPH assay, JC004, JC005, JC006, JC007, JC010, JCOIl and JC025 exhibited activities with EC50 values ranging from 28 µM to 178 µM while JC012, JC023 and JC024 did not exhibit any activity in the DPPH assay.

The analogues JC013, JC015 and JC021 exhibited minor anti-oxidant activity of 0.2 µmol TE/µmol, 0.5 µmol TE/µmol and 0.6 µmol TE/µmol respectively in the ORAC assay. None of these analogues exhibited any activity in the DPPH assay.

None of the capsaicin analogues tested demonstrated cytotoxicity at concentrations of up to 350 µM except for analogues JC024, JC025 and JC026, which exhibited slight cytotoxicity in HepG2 cell lines. JC024 and JC026 having IC50 values of 304 µM and 254 µM respectively, were less cytotoxic when compared to capsaicin, which has an IC50 of 178 µM in HepG2 cell lines. JC025 having an IC50 of 125 µM was slightly more cytotoxic than capsaicin.

In addition, the capsaicin analogues disclosed herein, particularly analogues JC005, JC006, JC007, JC010, JC011, JC012, JC013, JC014, JC015, JC016, JC017, JC018, JC022, JC023, JC024, JC025 and JC026, were easily obtained through a simple synthetic procedure at a reduced cost compared to the high cost of isolating capsaicin from chili pepper. Those capsaicin analogues with no cytotoxicity can be used as potent anti-oxidative agents in medicine, health supplements, cosmetic
formulations, and stabilizers in food, cosmetics and personal care products.

**Comparative Example 2**

Comparison of Anti-oxidant Activity and Cytotoxicity of Analogues JC017 and JC058

Analogues JC017 and JC058 were synthesized based on the procedure set out in Example 3 above. Analogue JC058 has the same structure as analogue JC017 except that the oxygen at the 'z' position of formula (I) is replaced with a sulfur in JC058. The structures of both analogues are shown in Table 3 below.

The anti-oxidant activities of both analogues JC058 and JC017 were analyzed using the ORAC and DPPH assays as set out above. The cytotoxicity of both analogues JC058 and JC017 were also assayed using the HepG2 and A549 cell lines according to the protocol set out above.

The anti-oxidant activities and cytotoxicity of both analogues are set out in Table 3 below.
Table 3. Antioxidant Activities and Cytotoxicities of Analogues JC017 and JC058

<table>
<thead>
<tr>
<th>Sample Code</th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
<th>ORAC (μmol TE/μmol) (n=5)</th>
<th>DPPH EC50 (μM) (n=5)</th>
<th>Cytotoxicity in A549 IC50 (mM) (n=4)</th>
<th>Cytotoxicity in HepG2 IC50 (mM) (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JC017</td>
<td><img src="image" alt="Structure" /></td>
<td>C_{14}H_{22}N_{2}O_{3}</td>
<td>266.16</td>
<td>6.57±0.03</td>
<td>37±4.2</td>
<td>&gt;1.5</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>JC058</td>
<td><img src="image" alt="Structure" /></td>
<td>C_{14}H_{22}N_{2}O_{5}S</td>
<td>282.14</td>
<td>6.53±1.75</td>
<td>19±0.7</td>
<td>0.49±0.1</td>
<td>0.9±0.1</td>
</tr>
</tbody>
</table>
From Table 3 above, the anti-oxidant activities of the two analogues appear to be comparable. However, from a comparison of the cytotoxicity of the two analogues, analogue JC017 clearly exhibits significantly lower cytotoxicity than analogue JC058 in both the HepG2 cell line as well as in the A549 cell line. Hence, the data indicates that substitution of the sulfur atom on the carbonyl group of analogue JC058 with an oxygen atom in analogue JC017 confers the advantage of reducing the cytotoxicity of the compound while maintaining high anti-oxidant activity.

The dose response curves for analogue JC017 in a cytotoxicity assay using the cell lines HepG2 and A549 are shown in Fig. 1 while the dose response curves for analogue JC058 in a cytotoxicity assay using the cell lines HepG2 and A549 are shown in Fig. 2.

As can be seen from Fig. 1, when analogue JC017 was administered at varying concentrations to the HepG2 cell line, cell inhibition was relatively low, and ranged, on average, from 0% to about 40% after exposing the cell lines to varying concentrations of between 0.02 mM and 1.5 mM analogue JC017 for 24 hours. The IC50 of JC017 in the HepG2 cell line was higher than 1.5 mM.

In the dose-response curve of analogue JC017 in cytotoxicity assays on the A549 cell line for the same dosage range, there was no detectable cell inhibition even when doses of 1.5 mM were administered for 24 hours (Fig. 1). The IC50 of JC017 in the A549 cell line was also higher than 1.5 mM.

When analogue JC058 was administered at varying concentrations to the HepG2 and A549 cell lines, cell
inhibition showed a dose-response from concentrations of as low as 0.18 mM (Fig. 2). Cell inhibition as high as >90% was seen for a concentration of 1.5 mM after a 24-hour exposure to analogue JC058. The IC50 value of JC058 was 0.5 mM in the A549 cell line and 0.9 mM in the HepG2 cell line.

The dose-response curves for analogues JC017 and JC058 against the A549 cell line were compared in Fig. 3. It can be seen that, in the same concentration range, there was no detectable cell inhibition by analogue JC017, while the analogue JC058 showed high cell inhibition of upto >90% after a 24-hour exposure to 1.5 mM of JC058 (Fig. 3). In other words, analogue JC017 is not cytotoxic while analogue JC058 has comparatively high cytotoxicity.

Similarly, in a comparison of the dose-response curves for analogues JC017 and JC058 against the HepG2 cell line, it can be seen that cell inhibition by analogue JC017 was significantly lower than cell inhibition by analogue JC058 within the same concentration range tested (Fig. 4). In other words, analogue JC017 is less cytotoxic than analogue JC058.

In summary, analogues JC017 and JC058 both have comparably high anti-oxidant activity. Analogue JC017 has the added advantage of having low cytotoxicity.
Applications

The active compounds disclosed herein have demonstrated strong anti-oxidative activity. Advantageously, by providing strong anti-oxidative effect, the disclosed active compounds are useful as anti-oxidative agents. Accordingly, the disclosed active compounds are useful as anti-oxidative agents in medicines to treat a patient suffering from an oxidative stress related disorder or condition. The disclosed active compounds are also useful as anti-oxidative agents in health supplements and cosmetic formulations to prevent and delay aging caused by oxidative stress. The disclosed active compounds are furthermore useful as anti-oxidative agents for stabilizing food, cosmetics and personal care products against oxidative damage.

In addition, the disclosed active compounds have very low toxicity to humans and therefore are ideal for use in medicine, particularly for use in medicines for treating patients suffering from oxidative stress related disorders.

It will be apparent that various other modifications and adaptations of the invention will be apparent to the person skilled in the art after reading the foregoing disclosure without departing from the spirit and scope of the invention and it is intended that all such modifications and adaptations come within the scope of the appended claims.
Claims

1. A compound represented by the general formula
\[ \mathcal{D} : \]

\[ n(R_i) \]

and pharmaceutically acceptable salts thereof, wherein
- \( n \) is an integer from 1 to 5;
- \( p \) is an integer from 0 to 4;
- \( R_i \) is selected from the group consisting of a hydroxyl group, an alkoxy group, a thiol group, and a thioether group;
- \( R_2 \) and \( R_3 \) are independently a methylene group or a nucleophile, with the proviso that at least one of \( R_2 \) and \( R_3 \) is a nucleophile group;
- \( Z \) is an oxygen \( (O) \) atom or sulfur \( (S) \) atom;
- \( T \) is hydrogen or an optionally substituted aliphatic group;

with the proviso that when \( n = 2 \), \( R_i \) is not \(-\text{OCH}_3\) on the carbon-3 position of the phenyl group and \( R_i \) is not \(-\text{OH}\) on the carbon-4 position of the phenyl group.

2. A compound as claimed in claim 1, wherein \( Z \) is an oxygen \( (O) \) atom.
3. A compound as claimed in claim 1 or 2, wherein n is between 1 to 3.

4. A compound as claimed in any one of the preceding claims, wherein n is 2.

5. A compound as claimed in any one of the preceding claims, wherein n is 2 and R_i is on the carbon-3 position and the carbon-4 position of the phenyl group.

6. A compound as claimed in any one of claims 1 to 4, wherein n is 2 and R_i is on the carbon-2 position and the carbon-5 position of the phenyl group.

7. A compound as claimed in any one of the preceding claims, wherein n is 2 and each of R_i is -OH.

8. A compound as claimed in any one of claims 1 to 3, wherein n is 1 and R_i is on the carbon-4 position of the phenyl group.

9. A compound as claimed in any one of claims 1 to 3, wherein n is 1 and R_i is on the carbon-2 position of the phenyl group.

10. A compound as claimed in any one of the preceding claims, wherein p is 1.
11. A compound as claimed in any one of the preceding claims, wherein Ri is OU, wherein U is an alkyl group having from 1 to 6 carbon atoms.

12. A compound as claimed in any one of the preceding claims, wherein Ri is ZiTi, wherein Zi is a sulfur (S) atom or oxygen (O) atom and Ti is a lower alkyl group.

13. A compound as claimed in claim 12, wherein the lower alkyl has from 1 to 6 carbon atoms.

14. A compound as claimed in claims 1-6 and 8-13, wherein Ri is independently selected from the group consisting of -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂CH₃, -OCH₂CH₂CH₂CH₃, -OCH₂CH₂CH₂CH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -SCH₂CH₂CH₃, -SCH₂CH₂CH₂CH₃, -SCH₂CH₂CH₂CH₂CH₃, and -SCH₂CH₂CH₂CH₂CH₃.

15. A compound as claimed in claim 14, wherein n is 2 and one of Ri is -OH and the other of Ri is -OCH₃.

16. A compound as claimed in any one of the preceding claims, wherein T is an aliphatic group with 1 to 20 carbons.

17. A compound as claimed in claim 16, wherein T is an aliphatic group with 1 to 10 carbons.
18. A compound as claimed in claim 17, wherein T is an aliphatic group with 5 to 10 carbons.

19. A compound as claimed in any one of the preceding claims, wherein the aliphatic group of T is an alkyl.

20. A compound as claimed in claim 19, wherein the alkyl of T is straight or branched chain.

21. A compound as claimed in any one of claims 1 to 18, wherein the aliphatic group of T is an aliphatic group containing at least one unsaturated alkenyl or alkynyl group.

22. A compound as claimed in any one of the preceding claims, wherein T is an aliphatic group substituted with heteroatoms groups.

23. A compound as claimed in any one of claims 1 to 15, wherein T comprises an optionally substituted aryl group, heteroaryl group or cycloalkyl group.

24. A compound as claimed in any one of the preceding claims, wherein the nucleophile of R₂ and/or R₃ is selected from the group consisting of a halide, a nitrogen nucleophile, a sulfur nucleophile and an oxygen nucleophile.

25. A compound as claimed in claim 24, wherein the nitrogen nucleophile is an amino group.
26. A compound as claimed in claim 25, wherein the amino group is selected from the group consisting of NH, NHV and NW', where V and v' are each independently selected from the group consisting of a C1-C4 lower alkyl, a phenyl, and an alkoxy group.

27. A compound as claimed in any one of the preceding claims, selected from the group consisting of:
28. A pharmaceutical or cosmetic composition comprising as an active ingredient a compound of any one of the preceding claims and a pharmaceutically or cosmetically acceptable carrier.

29. A food preparation comprising a compound as claimed in any one of claims 1 to 27.

30. A compound of any one of claim 1 to 27 for use in the prevention and/or treatment of a condition associated with oxidative stress and/or a condition caused by presence of free radicals.
31. Use of a compound of any one of claims 1 to 27, in the manufacture of a medicament for the prevention and/or treatment of a condition associated with oxidative stress and/or a condition caused by presence of free radicals.

32. A method of preventing and/or treating a condition in a subject, wherein said condition is associated with oxidative stress and/or caused by presence of free radicals, said method comprising administering to said subject an effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 27.

33. The compound of claim 30, the use of claim 31, or the method of claim 32, wherein said condition is selected from the group consisting of aging, coronary heart disease, cardiovascular disease, cancer, stroke, neurodegenerative disease, inflammatory conditions, respiratory disease, digestive disease, hepatic disease, immune disease and diabetes.
Fig. 1

JC017: Hep G2 & A549 Cytotoxicity

% inhibition

A549
HepG2

Concentration log[mM]
Fig. 2

JC058: Hep G2 & A549 Cytotoxicity

% Inhibition

0.010  0.100  1.000  10.000
Concentration log [mM]
Fig. 3

Comparison cytotoxicity of JC017 & JC058 in A549 cell line

% inhibition

-50  -30   -10    10    30    50    70    90    110

Concentration log[mM]

JC058
JC017
Fig. 4

Comparison cytotoxicity of JC017 & JC058 in HepG2 cell line.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.
C07C 275/24 (2006.01) A61P 9/00 (2006.01) A67P 59/06 (2006.01)
A23L 1/30 (2006.01) A61P 11/00/2006.01) C07C 255/34 (2006.01)
A61K 31/165 (2006.01) A61P 17/18 (2006.01) C07C 335/12 (2006.01)
A61K 31/17 (2006.01) A61P 19/00 (2006.01) C07Z 2/5/56 (2006.01)
A61P 1/00 (2006.01) A61P 25/00 (2006.01) C07D 213/59 (2006.01)
A61P 7/02 (2006.01) P 55/00 (2006.01) C07D 317/760 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS Online - File Registry and CAPlus: Structure search based on exemplified compounds

Google - Using keywords "capsinoid AND antioxidant"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C  See patent family annex

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search 18 August 2010

Date of mailing of the international search report 25 AUG 2010

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Form PCT/ISA/210 (second sheet) (July 2009)
**C (Continuation).**

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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

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