

Improvements in pharmaceutical compositions

Description

5 The present invention relates to certain cyclopentanone and cyclopentenone derivatives. It also relates to the preparation of such derivatives, and to their use in medicine and other fields. The invention further relates to certain cyclopentanone derivatives with enhanced water solubility and therapeutic indices, and to methods of enhancing the water solubility and therapeutic indices of pharmaceutically active
10 cyclopentenone derivatives.

Various compounds comprising the cyclopentenone ring structure (also known as the cyclopentenone nucleus) are capable of inducing the heat shock response. The heat shock response is a finely regulated and highly conserved mechanism to protect
15 cells against different types of injury, including extreme temperatures, oxidative stress, exposure to toxins and viral infection (1). In human cells, triggering of the heat shock response requires activation of a transregulatory protein, the heat shock transcription factor type 1 (HSF 1), which controls the expression of cytoprotective heat shock proteins (HSPs) (1). Whereas HSP induction was at first interpreted as a
20 signal for detection of physiological stress, it is now accepted that HSPs are utilised by cells as molecular chaperones in the repair process following different types of injury to prevent damage resulting from the accumulation and aggregation of non-native proteins (1). In particular, a cytoprotective role of the heat shock protein HSP70 has now been described in a wide variety of human diseases, including
25 ischemia, inflammation and viral infection (2-5). For these reasons HSF 1 is considered a novel, attractive target for cytoprotective and antiviral drugs. In the case of viral infection, Santoro *et al.* have shown that a class of prostaglandins (PGs) with potent antiviral activity function as HSP70 inducers via HSF1 activation (6,7).

30 The ability of prostaglandins of the A type (PGAs) to inhibit viral replication and prevent the establishment of persistent infections was first reported in 1980 (8). It is now well established that PGs containing an α , β -unsaturated carbonyl group in the cyclopentane ring structure (cyclopentenone PG, cyPG) possess activity against

a wide variety of DNA and RNA viruses, including herpes viruses, paramyxo viruses, orthomyxo viruses and retroviruses in *in vitro* and *in vivo* experimental models (9). The mechanism of the antiviral activity is distinct from any other known antiviral agent and is thought to involve the induction of heat shock proteins and the inhibition of the transcription factor NF- κ B (nuclear factor- κ B) in the infected cell.

NF- κ B is an inducible eukaryotic transcription factor which has a critical role in promoting inflammation and viral replication (11). In most cells, NF- κ B exists in an inactive cytoplasmic complex, whose predominant form is a heterodimer composed of p50 and p65 subunits, bound to inhibitory proteins of the I κ B family, usually I κ B α , and is activated in response to primary (viruses, bacteria, UV) or secondary (inflammatory cytokines) pathogenic stimuli (12). Stimulation triggers rapid phosphorylation and degradation of I κ B α , resulting in NF- κ B translocation to the nucleus, where the factor binds to DNA at specific κ B-sites, inducing a variety of genes encoding signalling proteins. Target genes include those coding for inflammatory and chemotactic cytokines, cytokine receptors and viral proteins. NF- κ B is involved in many pathological events including progression of AIDS by enhancing HIV-1 transcription and is considered an attractive therapeutic target for novel antiviral and anti-inflammatory drugs (12). Santoro *et al.* have shown that cyclopentenone prostaglandins inhibit NF- κ B activation and NF- κ B dependent HIV-1 transcription in human cells, by preventing I κ B α phosphorylation and degradation, and that this effect is strictly associated with HSF1 activation (11).

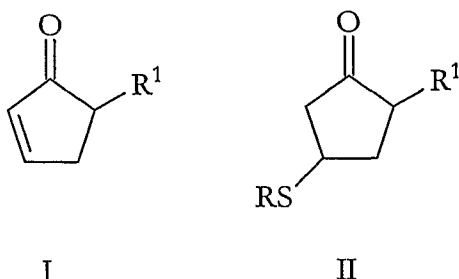
Santoro *et al.* have identified the molecular structure of natural prostaglandins responsible for HSF activation and NF- κ B inhibition (13). One component of the PGA molecule, cyclopent-2-en-1-one (also known as 2-cyclopenten-1-one), at a concentration of 125-500 μ M, has been shown to be able to activate HSF1 and to rapidly and selectively trigger the synthesis of cytoprotective HSP70. At the same concentration, cyclopent-2-en-1-one has been shown to be able to block NF- κ B activation by chemical or physiological inducers. These effects are associated with antiviral activity during infection with rhabdoviruses (13).

A family of pharmaceutically active cyclopent-2-en-1-one derivatives is described in International patent application no. PCT/GB00/01086, published as WO00/56341. The experimental results set out in this document show members of this family of compounds to be potent activators of HSF and inhibitors of NF- κ B activity. They
5 also show such compounds to be potent inhibitors of HSV-1 and Sendai virus replication. All of the compounds disclosed in this reference include a group -OX bound to the carbon atom in the 4 or 5 position in the cyclopentenone ring, in which X can be an alkyl, aryl or aralkyl group, or an alkyl, aryl or aralkyl substituted silyl group. A further family of pharmaceutically active cyclopentenone derivatives
10 is described in International application no. PCT/GB00/04868, published as WO01/44254. Members of this family also comprise a cyclopent-2-en-1-one ring with a similarly defined group -OX bound to the carbon atom in the 4 position in the ring. They also include a double bond to the carbon atom in the 5 position in the ring, α to the carbonyl carbon.

15 There is no suggestion in the literature that any cyclopentenone derivatives, other than the natural prostaglandins and those substituted in either or both of the 4 and 5 positions in the cyclopentenone ring with an oxy moiety, have a capacity to exhibit biological activity of the above discussed nature.

20 Surprisingly, it has now been found that certain cyclopentenone derivatives, in which neither of the carbon atoms in the 4 and 5 positions are bound to an oxygen atom and which do not include both prostaglandin like side chains, are pharmaceutically active in at least one of the aforementioned ways.

25 According to the present invention, there is provided a compound of formula I or II:-



wherein:

R is a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, aralkyl
aralkenyl, or aralkynyl group, that optionally includes at least one heteroatom in its
5 carbon skeleton; and,

R¹ is a substituted or unsubstituted, branched or straight chain alkyl, alkenyl,
or alkynyl group, that contains 1-12 carbon atoms.

R can be an R²CH₂- group, wherein R² is a substituted or unsubstituted alkyl,
10 alkenyl, alkynyl, aryl, aralkyl aralkenyl, or aralkynyl group, that optionally includes at
least one heteroatom in its carbon skeleton. R, preferably, contains 1-12 carbon
atoms.

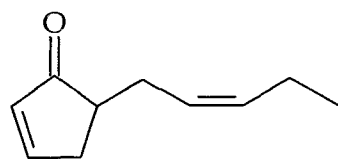
In preferred embodiments, R includes at least one hydrophilic group. Said
15 hydrophilic group can be or include a hydroxyl, carbonyl, carboxyl, amino, amido,
quaternary ammonium or thiolyl group. R, therefore, can provide the functionality
of an amine, amide, peptide, ester, carboxylic acid, carboxylic acid salt, alcohol,
aldehyde, ketone or thiol to an inventive compound.

20 In further preferred embodiments, the group -SR is an S-cysteinyl or a substituted
S-cysteinyl group. In the context of this application, a substituted or unsubstituted
S-cysteinyl group comprises a cysteinyl moiety that is bound to the ring via its
sulphur atom, with the ring replacing the hydrogen atom that is bound to the
equivalent sulphur atom in cysteine. Preferred substituted S-cysteinyl groups
25 include di- and tri-peptide groups that include an S-cysteinyl moiety, such as S-
glutathionyl, S-cysteinyl ester and other like groups, including N-tert-
butoxycarbonyl S-cysteinyl and N-tert-butoxycarbonyl S-cysteinyl ester (e.g. methyl
and ethyl) groups.

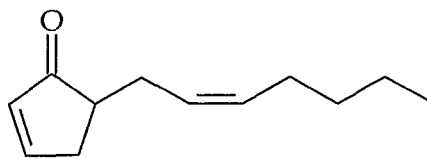
Preferably, R^1 includes up to 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms and, preferably, at least 4 carbon atoms. R^1 is preferably unsubstituted. In preferred embodiments of the invention, R^1 is unsaturated, preferably unbranched, preferably an alkenyl group, and can include a single double bond between the second and third carbon atoms from the cyclopentenone ring in formula I, or the cyclopentanone ring in formula II. When the R^1 carbon chain includes such a double bond, it is preferably in the cis- or (Z) form, although it can be in the trans- or (E) form. In more preferred embodiments, R^1 includes 5, 7, or 12 carbon atoms. Thus, in preferred
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embodiments, R^1 is $-\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_n\text{CH}_3$ and n is 0-8. n is preferably 1, 2, 3, 4, 5, 6, 7, or 8 and most preferably 1, 3 or 8.

Certain compounds in accordance with the invention can exist in the form of a least two enantiomers and all such enantiomers, unequal mixtures thereof and racemates, are encompassed by the present invention. Both R- and S-enantiomers of these
15
compounds are useful. They can each be provided in a form substantially free of the other enantiomer (e.g. at least 75%, 85%, 90%, 95% or 99% free (w/w)). Mixtures of enantiomers (e.g. racemic mixtures) may however also be used.

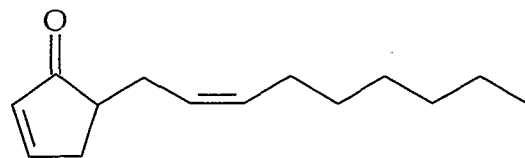
20 Preferred compounds in accordance with the present invention include the following: -



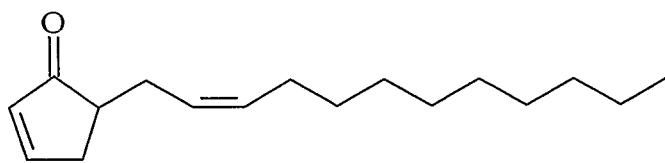
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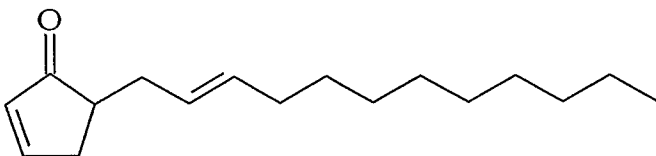
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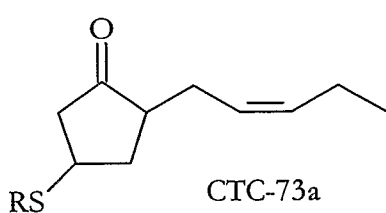
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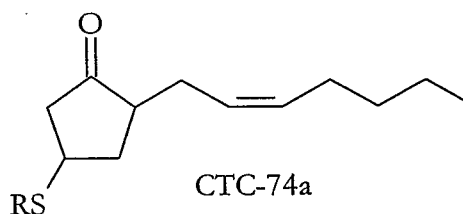
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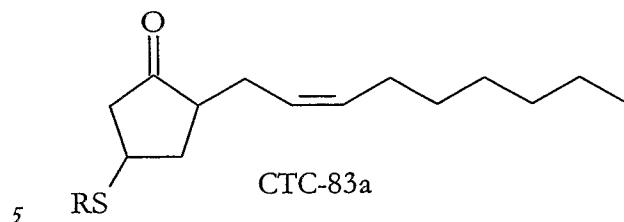
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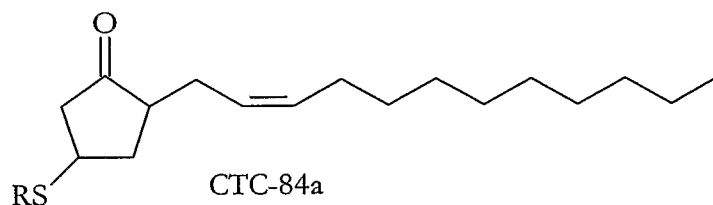
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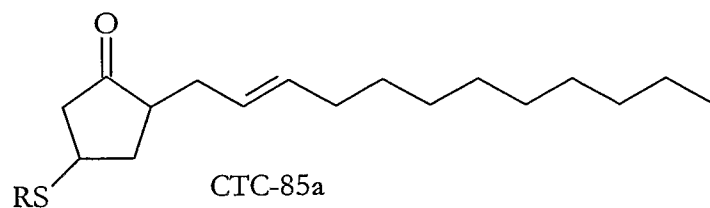
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CTC-83a



CTC-84a



CTC-85a

In the foregoing formulae, R is as defined above.

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Compounds in accordance with the invention may be prepared by the techniques described in the examples. In particular, compounds that include the group RS- may be prepared from their cyclopent-2-en-1-one analogues by a technique of the type described in the second general method B (see below). The required cyclopent-

2-en-1-one analogues can be prepared by a technique of the nature described in Examples 1-4.

Compounds in accordance with the invention preferably are capable of one or more
5 of the following:

- a) activating HSF
- b) inhibiting NF- κ B
- c) inhibiting the replication of HSV-1
- d) inhibiting the replication of Sendai virus.

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A skilled person can readily assay for the above activities and examples of suitable assays are set out in Examples 6 and 7 below.

Compounds that have greater activity in at least one of the foregoing respects than
15 cyclopent-2-en-1-one (at least at certain concentrations) represent preferred
embodiments of the invention; those that enjoy such activity at a concentration
within the range of 1-200 μ M, or over the whole or a part of said range, being
particularly preferred. Preferably, compounds in accordance with the invention
have a level of activity in at least one of the foregoing respects that is at least twice
20 the level of cyclopent-2-en-1-one. More preferably, it is at least 10 times that of
cyclopent-2-en-1-one.

Activity in one of the above respects is indicative of a compound's capacity to be
pharmaceutically active. Accordingly, in a yet further aspect, the present invention
25 provides a compound in accordance with the invention for use in medicine
(including veterinary medicine). Preferred such uses include the treatment of the
human or animal body by therapy and diagnostic methods practised upon the
human or animal body. The treatment may be prophylactic or may be in respect of
an existing condition. Therapeutic (including prophylactic) and diagnostic methods,
30 involving the use of a compound in accordance with the invention, are also within
the remit of the invention.

The use of such compounds for the manufacture of medicaments for use in therapeutic or diagnostic methods to be practised on the human or animal body, lie within the scope of a further aspect of the invention.

5 The preferred uses for compounds in accordance with the invention include the treatment of disorders which can be treated in a host by the activation of a heat shock transcription factor (e.g. HSF1), by the induction of heat shock proteins (e.g. hsp70) and/or by the inhibition of NF- κ B. Certain preferred compounds in accordance with the invention can be used in therapeutic applications that involve
10 activating HSF and inhibiting the activity of NF- κ B.

Thus, in accordance with the invention, compounds in accordance with the invention can be used to treat diseases or conditions in which such activity is indicated or can be of advantage. They can also be used in the manufacture of
15 medicaments for use in such treatments. The preferred therapeutic and diagnostic applications for the inventive compounds are discussed in detail below.

Many pharmaceutically active compounds are poorly soluble in water or highly lipophilic. Such compounds are less suited, therefore, to being administered to
20 patients orally than by other routes of administration, that are generally less favoured by patients, such as by parenteral injection.

The therapeutic index of a drug or pharmaceutically active compound is indicated by the ratio of its median lethal dose, or LD₅₀, to its medium effective dose, or
25 ED₅₀. Because its use would generally involve a lower risk of causing toxic side effects in individual patients given a therapeutically effective dose, a compound with a larger therapeutic index would normally be preferred over an alternative with a smaller therapeutic index. Accordingly, if the therapeutic index of a particular pharmaceutically active compound could be increased without ill effect, this would
30 be an attractive result.

Preferred compounds of formula II are:-

- (a) more soluble in water at a temperature of 20-40°C;

- (b) less lipophilic; and/or,
- (c) have a greater therapeutic index;

than equivalent compounds of formula I. An equivalent compound of formula I to a preferred compound of formula II is a compound with, excepting the absent -SR
5 group and an additional hydrogen atom in the 2 position in the five membered ring, the same substitution pattern as the preferred compound of formula II.

Where a preferred compound in accordance with the invention is required to be less lipophilic than an "equivalent" compound, this means that the ratio of *n*-octanol to
10 aqueous solubility (i.e. the *n*-octanol/water partition coefficient) for the preferred compound is lower than it is for the "equivalent" compound. This ratio is usually expressed in terms of its base ten logarithm, "logP", and a compound with a logP value of 1 will be 10 times more soluble in *n*-octanol than it is in water, a compound with a logP value of 2 will be 100 times more soluble in *n*-octanol than it is in water
15 and so on. LogP values can be measured by experiment, or calculated using one of several available computer programs or algorithms. Examples of these include the Pomona College Medicinal Chemistry program and the method described by Moriguchi et al.(20). Thus, it is preferred that compounds, required in this specification to be more lipophilic than equivalent compounds, will have lower logP
20 values than such equivalents. In this context, the logP values are preferably calculated values derived from applying one of the aforementioned programs or algorithms.

Where a preferred compound in accordance with the invention is required to have a
25 greater therapeutic index than an "equivalent", this relationship must hold true for at least one therapeutic application. For the purposes of this specification, the existence of such a relationship can be established either by observation of *in vivo* effects, or via *in vitro* tests or assays of the type conventionally employed by persons skilled in the art for the purpose of predicting the therapeutic indices of putative
30 drug substances. For example, an assay for one of the properties discussed below could be used in combination with a toxicity assay, to provide the required information for a particular pair of inventive compound and equivalent. Examples of appropriate assays are set out in Examples 6-8 below.

In preferred embodiments, the preferred compounds of formulae II will have a calculated or measured logP value that is at least 0.25, 0.5, 0.75, 1 or 1.25 lower than the logP value for their equivalents of formula I, wherein the logP values for the
5 compounds are calculated or measured using the same technique. Preferably, the preferred compounds of formula II have a logP value of 5 or less, and preferably of 4.15 or less when calculated by the method described by Moriguchi et al. (20).

Compounds with logP values in these latter preferred ranges are generally more readily absorbed from the gastro-intestinal tract and, therefore, are more suited to
10 oral administration. See Lipinski et al. (21).

An advantage of the preferred compounds of formula II are that, because they are less lipophilic and/or more soluble in water at around room temperature and/or body temperature than are their equivalents of formula I, that do not include an
15 -SR substituent, they are more suited to use in orally administered pharmaceutical compositions. Moreover, because such compounds of formula II can also have a greater therapeutic index than their equivalents without an -SR substituent, they are potentially more useful in a therapeutic context.

20 Cyclopentenone compounds are known to undergo Michael reactions with glutathione in the cell. Glutathione is found throughout the body and plays crucial roles in protecting cells from oxidative damage (maintaining redox balance). In this regard, work by Uchida et al. (22) and others has suggested a role for glutathione in protecting cells from oxidative stress as a radical scavenger. Uchida's work showed
25 that cells with depleted glutathione retain higher concentration of radical oxygen species. It also demonstrated that, when such cells were treated with N-acetyl-cysteine and cell viability was measured, an increase in cell life and a decrease in the production of radical oxygen species was observed. Uchida et al. came to the conclusion that species capable of reducing glutathione levels in the cell, also reduce
30 the cell's anti-oxidant defences and increase the induction of radical oxygen species. They also showed that cyclopentenone mediated production of radical oxygen species was well correlated with cytotoxicity and, thus, demonstrated a potentially

important mode of cytotoxicity or induction of cell death by cyclopentenone compounds.

Glutathione is also known to protect cells from dangerous electrophilic species.

5 For example, morphine type compounds undergoes a Michael reaction with glutathione that results in complete deactivation of the drug (23). If large amounts of paracetamol (acetaminophen) are taken then glutathione in the liver is depleted [in 1999 there were 150 deaths in the UK from paracetamol poisoning]. If *N*-acetyl
10 cysteine is taken intravenously or orally less than 15 h after the overdose it effectively removes the offending electrophilic paracetamol metabolite (24).

Other studies have shown that a reduction of intracellular thiol content can increase the sensitivity of tumour cells to radiation treatment. Moreover, cells exhibiting
15 depleted levels of glutathione have been shown to be more susceptible to radiation, chemotherapeutic agents and oxygen radical species that otherwise would have been destroyed via radical reaction with glutathione (25).

A glutathione group cannot be added to a saturated moiety, such as a cyclopentanone group, via a Michael reaction. Thus, unless they are metabolised
20 into the equivalent unsaturated cyclopent-2-en-1-ones, compounds in accordance with the invention that comprise a cyclopentanone group may be less likely to react with glutathione *in vivo* than are these unsaturated equivalents. Such saturated compounds, therefore, may be less likely to deplete the levels of glutathione in a
25 patient's cells, and thereby compromise their anti-oxidant defences, than the equivalent cyclopent-2-en-1-one derivatives. Without wishing to be bound by theory, this may explain why some compounds in accordance with the invention that include an -SR group have significantly enhanced therapeutic indices, in addition to enhanced water solubility and reduced lipophilicity.

30 Without again wishing to be bound by theory, it is considered that compounds in accordance with the present invention, wherein the carbon atom in the 3 position in their cyclopentanone rings carries an -SR group, enjoy their enhanced properties partially because they can act as pro-drugs for the equivalent cyclopent-2-en-1-ones,

in the sense that it is thought that they are converted into the latter *in vivo*. In this regard, it is considered that, before it is cleaved, the group –SR renders these compounds more water soluble and less lipophilic than their equivalents, and hence more suited to oral delivery, and that *in vivo* cleavage of the –SR group releases, via a
5 reverse Michael reaction, the more potent cyclopent-2-en-1-one equivalent.

Thus, in embodiments, compounds of formula II in accordance with the invention are transformable into equivalent cyclohex-2-en-1-one derivatives of formula I by a reverse Michael reaction, or are pro-drugs for such equivalents.

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In further preferred embodiments, the group –SR is an S-cysteinyl or a substituted S-cysteinyl group. Preferred substituted S-cysteinyl groups include di- and tri-peptide groups that include an S-cysteinyl moiety, such as S-glutathionyl, S-cysteinyl ester and other like groups, including N-tert-butoxycarbonyl S-cysteinyl and N-tert-
15 butoxycarbonyl S-cysteinyl ester (e.g. methyl and ethyl) groups.

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Without once again wishing to be bound by theory, it is considered that compounds in accordance with these latter embodiments of the invention are also capable of providing a secondary therapeutic effect resulting from their incorporation of a
20 substituted or unsubstituted cysteinyl moiety. For example, when acting as pro-drugs in the aforementioned manner, such compounds may be capable of delivering both the equivalent cyclopent-2-en-1-one derivative and the reduced form of the substituted or unsubstituted cysteinyl moiety to target cells in a patient's body, where both may exert their therapeutic effects. The therapeutic effect exerted by
25 the reduced form of the substituted or unsubstituted cysteinyl moiety can be the prevention of glutathione depletion, especially when the reduced moiety is glutathione, an analogue or precursor. For example, the reduced, substituted or unsubstituted cysteinyl moiety may compete with native glutathione, to reduce the amount of the latter that is bound by the cyclopent-2-en-1-one derivative (formed
30 after *in vivo* cleavage) or a metabolite, or it may replace or lead to the replacement of glutathione bound by the derivative or a metabolite. Such activity is thought to contribute significantly to the reducing the toxicity of the inventive compounds and,

hence, to the increased therapeutic indices enjoyed by these compounds, in comparison to the equivalent cyclopent-2-en-1-one.

In a further embodiment of the present invention, there is provided a method of decreasing the lipophilicity and/or increasing the water solubility and/or the therapeutic index of a pharmaceutically active compound of formula I as defined above, said method comprising forming an adduct of said compound of formula I and a thiol of the formula HSR, wherein R is as herein before defined and the adduct is of formula II, as defined above.

The adduct may act as a pro-drug in the manner discussed above, or it may be pharmaceutically active in its own right.

In preferred embodiments of this method, the adduct is formed via a Michael reaction between the unsaturated compound of formula I and the thiol. A preferred method of forming the adduct is described in the examples that follow.

In a further aspect, the present invention provides an adduct as herein before defined, prepared or preparable by a method in accordance with the invention.

For the avoidance of doubt, it is confirmed that the term "alkenyl" denotes an a group with one or more double bonds in its carbon skeleton and the term "alkynyl" denotes a group with one or more triple bonds in its carbon skeleton. It should also be understood that, for the purposes of this specification, alkynyl groups may include both double and single bonds in their carbon skeletons. Unless otherwise specified, groups referred to in this specification as alkyl, alkenyl or alkynyl groups can be straight chained or branched, or be or include cyclic groups. However, unless the contrary is indicated, they are preferably straight chained or branched.

Medical uses for compounds in accordance with the invention

The preferred uses for compounds in accordance with the invention include the treatment of disorders which can be treated in a host by the activation of a heat

shock transcription factor (e.g. HSF1), by the induction of heat shock proteins (e.g. hsp70) and/or by the inhibition of NF- κ B.

Certain preferred compounds in accordance with the invention can be used in
5 therapeutic applications that involve activating HSF and inhibiting the activity of
NF- κ B. Thus, in accordance with the invention, such compounds can be used to
treat diseases or conditions in which such activity is indicated or can be of
advantage. They can also be used in the manufacture of medicaments for use in
such treatments. Preferred therapeutic and diagnostic applications for such
10 compounds are discussed below.

It should be appreciated that certain compounds in accordance with the invention
do not exhibit activity in all of the respects discussed above. Such compounds,
therefore, may only find use in those of the therapeutic and diagnostic applications
15 detailed below where their properties are indicative of potential usefulness.

It should be appreciated that certain disorders, e.g. cancers, may be mediated by
viruses and by non-viral factors. In the absence of any indication to the contrary,
treatment of any given disorder is covered whether or not the disorder is mediated
20 by viruses. It should also be appreciated that there is some overlap between the
various categories of treatment discussed, i.e. the categories are not intended to be
mutually exclusive.

1. *Treatment of viral-mediated disorders*

25 NF- κ B is implicated in the pathogenesis of certain viral infections. It is known that
heat shock proteins (e.g. HSP70) can offer protection against the pathogenesis of
viral infection. Compounds in accordance with the invention may be active in
reducing the replication of viruses.

30 Compounds in accordance with the invention may be useful in treating viral-
mediated disorders. These include disorders mediated by RNA viruses, as well as
disorders mediated by DNA viruses.

Examples of viral disorders that may be treated using compounds in accordance with the invention include the following.

Diseases caused by or associated with members of the *Adenoviridae* family, including
5 (but not limited to): diarrhea or intussusception caused by or associated with enteric
adenoviruses, upper or lower respiratory tract infections (including the common
cold or pneumonia) caused by or associated with respiratory adenoviruses;
conjunctivitis, keratitis or trachoma caused by or associated with adenovirus
infection of the eye; tonsillar or kidney infections caused by or associated with
10 adenoviruses.

Diseases caused by or associated with members of the *Arenaviridae* family, including
(but not limited to): Lassa fever caused by Lassa fever virus; meningitis caused by or
associated with lymphocytic choriomeningitis virus; hemorrhagic fevers including
15 (but not limited to) those caused by Machupo virus, Junin virus, Sabia virus,
Guanarito virus or Tacaribe virus.

Diseases caused by or associated with members of the *Astroviridae* family, including
(but not limited to): diarrhea caused by or associated with astroviruses.
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Diseases caused by or associated with members of the *Bunyaviridae* family, including
(but not limited to): hemorrhagic fever with renal syndrome, hantavirus pulmonary
syndrome, or other diseases caused by or associated with hantaviruses including (but
not limited to) Hantaan virus, Puumala virus, Seoul virus, Dobrava virus, Sin
25 Nombre virus, bayou virus, Black Creek canal virus, New York 1 virus, Monogahela
virus, Andes virus, Laguna Negra virus; arbovirus infections including (but not
limited to) La Crosse encephalitis, California encephalitis, or other bunyavirus
infections; Rift Valley fever, sandfly fever, Uukuniemi or other arbovirus infections
associated with phleboviruses; Crimean-Congo hemorrhagic fever or other
30 infections caused by Nairoviruses.

Diseases caused by or associated with members of the *Caliciviridae* family or related
agents, including (but not limited to): hepatitis caused by or associated with

hepatitis E virus, diarrhea caused by or associated with caliciviruses or small round structured viruses.

5 Diseases caused by or associated with members of the *Coronaviridae* family, including (but not limited to): lower or upper respiratory tract infections (including the common cold) caused by or associated with coronaviruses; diarrhea, enterocolitis or gastroenteritis caused by or associated with coronaviruses or toroviruses.

10 Diseases caused by or associated with members of the *Filoviridae* family, including (but not limited to): hemorrhagic fevers caused by Ebola or Marburg viruses.

15 Diseases caused by or associated with members of the *Flaviviridae* family, including (but not limited to): arbovirus infections, fevers or encephalitides including (but not limited to) yellow fever, Kyansur Forest disease, Omsk hemorrhagic fever, other tick-borne encephalitis infections, Rocio, Japanese encephalitis, St. Louis encephalitis, West Nile virus infection, Murray Valley encephalitis, Dengue fever, or Dengue hemorrhagic fever caused by or associated with flaviviruses; hepatitis caused by or associated with hepatitis C virus.

20 Diseases caused by or associated with members of the *Hepadnaviridae* family, including (but not limited to): hepatitis caused by or associated with hepatitis B virus.

25 Diseases caused by or associated with members of the *Herpesviridae* family, including (but not limited to): orolabial herpes, genital herpes, herpetic dermatitis, herpetic whitlow, zosteriform herpes simplex, ocular disease, encephalitis or neonatal herpes caused by or associated with herpes simplex viruses types 1 or 2; chickenpox, shingles, zoster-associated pain, pneumonia, encephalitis, fetal infection or retinal necrosis caused by or associated with varicella-zoster virus; transplant rejection, 30 congenital infection, infectious mononucleosis, retinitis or other diseases of the immunocompromised caused by or associated with cytomegalovirus; infectious mononucleosis, lymphomas, carcinomas or other cancers caused by or associated with Epstein-Barr virus; exanthem subitum, roseola infantum, pneumonitis or

hepatitis caused by or associated with human herpesviruses 6 or 7; Kaposi's sarcoma or other neoplastic disease caused by or associated with human herpesvirus 8 (KSV).

- 5 Diseases caused by or associated with members of the *Orthomyxoviridae* family, including (but not limited to): influenza, pneumonia, other respiratory infections, myositis, myoglobinuria, or Reye's syndrome caused by or associated with influenza viruses A, B or C.
- 10 Diseases caused by or associated with members of the *Papovaviridae* family, including (but not limited to): papillomas, comdylomas, neoplasias and carcinomas caused by or associated with papillomaviruses; diseases caused by BKV or JCV viruses; progressive multifocal leukoencephalopathy caused by polyomaviruses.
- 15 Diseases caused by or associated with members of the *Parvoviridae* family, including (but not limited to): anemia, fever, fetal infection or hepatitis caused by or associated with parvorvirus B19.

- Diseases caused by or associated with members of the *Paramyxoviridae* family, including (but not limited to): pneumonia, bronchiolitis, tracheobronchitis or croup caused by or associated with parainfluenza viruses; bronchiolitis or pneumonia caused by or associated with respiratory syncytial virus; encephalitis, measles or complications of measles including (but not limited to) pneumonia or sub-acute sclerosing panencephalitis (SSPE) caused by or associated with measles virus;
- 20 mumps or complications of mumps including (but not limited to) orchitis or pancreatitis caused by or associated with mumps virus.

- Diseases caused by or associated with members of the *Picornaviridae* family, including (but not limited to): hepatitis caused by or associated with hepatitis A virus; upper
- 30 respiratory tract infections (including the common cold) caused by or associated with rhinoviruses or other respiratory picornaviruses; poliomyelitis caused by polioviruses; Bornholm disease, encephalitis, meningitis, herpangina, myocarditis,

neonatal disease, pancreatitis, fever, conjunctivitis, chronic fatigue syndrome (ME) or hand, foot and mouth disease caused by coxsackieviruses or enteroviruses.

5 Diseases caused by or associated with members of the *Poxviridae* family, including (but not limited to): smallpox caused by smallpox virus; human forms of monkeypox or cowpox virus infections; infections with vaccinia virus including (but not limited to) complications of vaccination; orf or paravaccinia caused by parapoxviruses; molluscum contagiosum caused by molluscipoxviruses; infections with Tanapox virus.

10

Diseases caused by or associated with members of the *Reoviridae* family, including (but not limited to): diarrhea caused by or associated with rotaviruses.

15

Diseases caused by or associated with members of the *Retroviridae* family, including (but not limited to): acquired immune deficiency syndrome and associated disorders caused by or associated with human immunodeficiency virus (HIV); leukaemias, lymphomas, or myelopathies caused by or associated with HTLV viruses.

20

Diseases caused by or associated with members of the *Rhabdoviridae* family, including (but not limited to): rabies caused by rabies virus; other lyssavirus diseases including (but not limited to) those caused by Duvenhage or Mokola viruses.

25

Diseases caused by or associated with members of the *Togaviridae* family, including (but not limited to): rubella or congenital rubella syndrome caused by rubella virus; fever or encephalitis caused by eastern equine encephalitis virus, Venezuelan equine encephalitis virus, western equine encephalitis virus, Everglades virus or Semliki Forest virus; fever, rash, polyarthrititis, myalgia or arthralgia caused by Sindbis virus, Ockelbo virus, Ross River virus, Barmah Forest virus, Chikungunya virus, O'nyong-nyong virus, Mayaro virus or Igo Ora virus.

30

Diseases caused by or associated with viroid-like agents, including (but not limited to): hepatitis caused by or associated with the delta agent (HDV).

Diseases caused by or associated with prions, including (but not limited to):
Creutzfeld-Jakob disease (CJD), new variant CJD, GSS, and fatal familial insomnia.

Compounds of the present invention may be particularly useful in treating viral and
5 other disorders affecting aquatic organisms (e.g. fish, crustaceans, etc.). Such
disorders include disorders mediated by the snout ulcer virus, by the iridovirus, by
the lymphocystis disease virus, etc.

Compounds in accordance with the invention may therefore be used in aquaculture.
10 They may be used in food for aquatic organisms. Such food is within the scope of
the present invention. It will generally be sold in sealed containers and labelled
appropriately (e.g. as fish food, food for crustaceans, food for aquatic organisms,
etc.). Alternatively, compounds in accordance with the invention may be used for
water treatment or for direct application to aquatic organisms. Such compounds do
15 not therefore need to be present in foodstuffs in order to be useful in aquaculture.

2. *Treatment of bacterial-mediated disorders*

NF- κ B is activated in response to bacterial infections.

20 Compounds in accordance with the invention can be useful in treating disorders
arising from such infections, e.g. in treating NF- κ B stimulated inflammation. Most
commonly this will arise due to infection with gram negative bacteria. However it
may also arise due to infection with gram positive bacteria (e.g. *S. aureus*).

25 3. *Treatment of disorders mediated by radiation*

NF- κ B is activated in response to radiation (e.g. UV-radiation).

Compounds in accordance with the invention can be useful in treating disorders
mediated by radiation. Such disorders include cell and tissue trauma, cell and tissue
30 ageing and cancer (e.g. skin cancer).

4. *Treatment of inflammation and of disorders of the immune system*

NF- κ B is activated in response to inflammatory cytokines. It is believed to be an early mediator of the immune and inflammatory responses.

5 Compounds in accordance with the invention can be useful in treating immune disorders (e.g. auto-immune disorders) and in treating inflammatory disorders. Examples of specific inflammatory disorders and disorders of the immune system that may be treated with such compounds include psoriasis, rheumatoid arthritis, multiple sclerosis, adult respiratory distress syndrome, hepatitis and/or cirrhosis, vascular inflammation (including lupus erythematosus disseminata), and
10 inflammatory disorders of the gastro-intestinal tract (e.g. ulcers).

5. *Treatment of Ischemia and Arteriosclerosis*

NF- κ B has been implicated in the pathogenesis of ischemia and arteriosclerosis. Compounds in accordance with the invention are therefore useful in treating such
15 disorders, including reperfusion damage (e.g. in the heart or brain) and cardiac hypertrophy.

6. *Treatment of disorders involving cell proliferation*

NF- κ B is implicated in cell proliferation.
20 Compounds in accordance with the invention can be useful as anti-proliferatives. They are therefore useful in treating inflammatory granulomas, neointimal proliferation in arterial and venous restenosis, and cancers (including lymphomas, leukemias, sarcomas, carcinomas and melanomas).

25

7. *Treatment of disorders involving damage to or killing of cells*

Heat shock proteins are known to provide a cytoprotective effect.

Compounds in accordance with the invention can be useful in treating disorders
30 involving damage to or killing of cells.

These disorders include chemical toxicity (e.g. due to ingestion of toxins, such as paraquat, or to overdosing with medicaments, such as paracetamol), oxidative cell

damage, cell and tissue ageing trauma, hepatitis diabetes and the effect of burns. The inventive compounds, also, can be used to combat the effects of ageing in a human or animal, and to promote wound healing.

- 5 Other conditions of this general nature, that can be treated using compounds of the present invention, include oxidative stress and degenerative diseases, especially neuro-degenerative diseases such as BSE, new variant CJD and Alzheimer's disease.

8. *Other treatments*

- 10 Cyclopentenone prostaglandins are of known utility in stimulating peroxisome proliferator activated receptors (PPARs). Compounds in accordance with the invention, thus, can be useful in treating diabetes (including complications arising therefrom). Such compounds can also be used in the treatment of disorders in which calcium loss or deficiency is implicated or involved (including bone disorders, skeletal disorders, dental disorders, developmental disorders, etc.).
- 15

9. *Treatments employing HSF selective compounds*

- Compounds in accordance with the present invention can exhibit a capacity to trigger a heat shock response, activate HSF, or induce HSP expression, at a concentration at which they have no significant inhibitory effect on NF- κ B activity.
- 20

- In the light of the reports discussed in the opening paragraphs of this specification (see references 6, 7, 11 and 13), suggesting that compounds that include a cyclopentenone nucleus and have a capacity to activate HSF will also inhibit the activity of NF- κ B, the selective action of compounds in accordance with the present invention is highly surprising. This unexpected property, however, renders these compounds uniquely useful in therapeutic applications where an effect upon the heat shock response is desirable, but any interruption of the normal NF- κ B pathway would be unnecessary, undesirable or possibly deleterious. For example, because the NF- κ B pathway plays an important role in T-cell mediated immune responses, its interruption could be immunosuppressive and, therefore, unless required in order to achieve a particular therapeutic objective, in principle should be avoided. Thus, these compounds can be particularly useful in the treatment of viral infections in
- 25
- 30

which the pathology of the virus does not involve an inflammatory component, or in which the killing of cells by the virus is more important in the pathology than is any inflammatory response. Such viruses include those that do not depend upon NF- κ B for their replication or do not have κ B elements in their genomes. In
5 addition to viral infections, HSF selective compounds can be used to treat other conditions which do not involve an inflammatory component, and they are particularly useful in cytoprotective applications.

Their selectivity allows HSF selective compound to be used in situations where it is
10 desirable for an NF- κ B mediated inflammatory immune response to be maintained. For example, they are especially useful in chronic or prophylactic treatments, as long term suppression of NF- κ B activity and, consequently, of a patient's full immune response to infection, can lead to unwanted opportunistic infections. It is also known that long term suppression of NF- κ B activity can cause apoptosis in the
15 liver.

Thus, the HSF selective compounds in accordance with the invention can be used in therapeutic applications that involve activating HSF without significantly inhibiting the activity of NF- κ B. Therefore, in accordance with the invention, these
20 compounds can be used to treat diseases or conditions in which such activity is indicated or can be of advantage. They can also be used in the manufacture of medicaments for use in such treatments.

Heat shock proteins are known to provide a cytoprotective effect. Thus, HSF
25 selective compounds can be useful in cytoprotective applications and in treating (including by prophylaxis) disorders involving damage to or killing of cells.

These disorders include chemical toxicity (e.g. due to ingestion of toxins, such as paraquat, or to overdosing with medicaments, such as paracetamol), oxidative cell
30 damage, cell and tissue ageing trauma, hepatitis, diabetes and the effect of burns. These compounds, also, can be used to combat the effects of ageing in a human or animal, and to promote wound healing.

Other conditions of this general nature, that can be treated using HSF selective compounds, include oxidative stress and degenerative diseases, especially neuro-degenerative diseases such as BSE, new variant CJD and Alzheimer's disease.

- 5 The cytoprotective effect of HSF selective compounds also renders them useful in the treatment of ischemia and the damage resulting from episodes of ischemia and subsequent reperfusion. They can be employed to ameliorate the damaging effects of radiation and/or chemotherapy particularly, but not exclusively, when used in the treatment of cancer. These compounds can also be used to treat certain types of
10 ulcers within the gastrointestinal tract.

- As suggested in a foregoing section, compounds in accordance with the invention can be used as anti-viral agents. HSF selective compounds are useful, in general, in the treatment of viral infections wherein the pathological effects of the infecting
15 virus can be reversed or prevented by a heat shock response. In particular, they can be employed to treat viral infections in which an inflammatory component is not significantly involved in or essential to the pathology of the infecting virus, the pathology of the virus does not involve an inflammatory component, or the killing of cells by the virus is more important than any inflammatory response. Such
20 viruses include those that are not dependant upon NF- κ B for their replication, or do not have κ B elements in their genomes. Examples include parvoviruses, rotaviruses and those that infect the upper respiratory tract, including picornaviruses, coronaviruses and adenoviruses.

- 25 HSF selective compounds can also be used to treat infection with certain viruses that involve NF- κ B and inflammation in their pathology, as the effects of many such organisms are reversed or prevented by the heat shock response and there may be other reasons why it may not be appropriate to administer an agent that disrupts the NF- κ B pathway to a particular patient.

30

Examples of viral infections that can be treated with HSF selective compounds include infections with Picornaviruses (including Rhinoviruses and Hepatitis A virus), Reoviruses (including Rotavirus), Parvoviruses, Paramyxoviruses (including

Sendai virus), Rhabdoviruses (e.g. vesicular stomatitis virus and rabies viruses),
Filoviruses (e.g. Ebola virus), Adenovirus and Coronavirus. Viral infections with
pathologies that involve inflammation and the NF- κ B pathway, but which can be
responsive to treatment with compounds in accordance with the invention, include
5 Influenza virus infections.

Routes of Administration for compounds in accordance with the invention

A medicament will usually be supplied as part of a pharmaceutical composition,
10 which may include a pharmaceutically acceptable carrier. This pharmaceutical
composition will generally be provided in a sterile form. It may be provided in unit
dosage form. It will generally be provided in a sealed container, and can be
provided as part of a kit. Such a kit is within the scope of the present invention. It
would normally (although not necessarily) include instructions for use. A plurality
15 of unit dosage forms may be provided.

Pharmaceutical compositions within the scope of the present invention may include
one or more of the following: preserving agents, solubilising agents, stabilising
agents, wetting agents, emulsifiers, sweeteners, colourants, odourants, salts
20 (compounds of the present invention may themselves be provided in the form of a
pharmaceutically acceptable salt, as explained in greater detail below), buffers,
coating agents or antioxidants. They may also contain other therapeutically active
agents in addition to a compound of the present invention.

25 Compounds of the present invention may themselves be provided in any suitable
form, i.e. they may be used as such or may be used in the form of a
pharmaceutically effective derivative. For example they may be used in the form of
a pharmaceutically acceptable salt or hydrate. Pharmaceutically acceptable salts
include alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts
30 (e.g. calcium or magnesium salts) aluminium salts, zinc salts, ammonium salts (e.g.
tetra-alkyl ammonium salts), etc. Inorganic acid addition salts (e.g. hydrochlorides,
sulphates, or phosphates) or organic acid addition salts (e.g. citrates, maleates,
fumarates, succinates, lactates, propionates or tartrates) may be used.

Pharmaceutical compositions of the present invention may be provided in controlled release form. This can be achieved by providing a pharmaceutically active agent in association with a substance that degrades under physiological
5 conditions in a predetermined manner. Degradation may be enzymatic or may be pH-dependent.

Pharmaceutical compositions may be designed to pass across the blood brain barrier (BBB). For example, a carrier such as a fatty acid, inositol or cholesterol may be
10 selected that is able to penetrate the BBB. The carrier may be a substance that enters the brain through a specific transport system in brain endothelial cells, such as insulin-like growth factor I or II. The carrier may be coupled to the active agent or may contain/be in admixture with the active agent. Liposomes can be used to cross the BBB. WO91/04014 describes a liposome delivery system in which an
15 active agent can be encapsulated/embedded and in which molecules that are normally transported across the BBB (e.g. insulin or insulin-like growth factor I or II) are present on the liposome outer surface. Liposome delivery systems are also discussed in US Patent No. 4,704,355.

20 A pharmaceutical composition within the scope of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) routes. Such a composition may be prepared by any
25 method known in the art of pharmacy, for example by admixing one or more active ingredients with a suitable carrier. In preferred embodiments, compounds in accordance with the invention are formulated into oral dosage forms and, therefore, are preferably provided in tablet or capsule form.

30 Different drug delivery systems can be used to administer pharmaceutical compositions of the present invention, depending upon the desired route of administration. Drug delivery systems are described, for example, by Langer (Science 249, 1527 – 1533 (1991)) and Illum and Davis (Current Opinions in

Biotechnology 2m 254 – 259 (1991)). Different routes of administration for drug delivery will now be considered in greater detail.

(i) *Oral Administration*

5 Pharmaceutical compositions adapted for oral administration may be provided as capsules or tablets; as powders or granules; as solutions, syrups or suspensions (in aqueous or non-aqueous liquids); as edible foams or whips; or as emulsions. Tablets or hard gelatine capsules may comprise lactose, maize starch or derivatives thereof, stearic acid or salts thereof. Soft gelatine capsules may comprise vegetable oils,
10 waxes, fats, semi-solid, or liquid polyols etc. Solutions and syrups may comprise water, polyols and sugars. For the preparation of suspensions, oils (e.g. vegetable oils) may be used to provide oil-in-water or water-in-oil suspensions.

An active agent intended for oral administration may be coated with or admixed
15 with a material that delays integration and/or absorption of the active agent in the gastrointestinal tract (e.g. glyceryl monostearate or glyceryl distearate may be used).

Thus, the sustained release of an active agent may be achieved over many hours and, if necessary, the active agent can be protected from being degraded within the
20 stomach. Pharmaceutical compositions for oral administration may be formulated to facilitate release of an active agent at a particular gastrointestinal location due to specific pH or enzymatic conditions.

(ii) *Transdermal Administration*

25 Pharmaceutical compositions adapted for transdermal administration may be provided as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis. (Iontophoresis is described in *Pharmaceutical Research*, 3(6):318 (1986).

30

(iii) *Topical Administration*

Pharmaceutical compositions adapted for topical administration may be provided as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays,

aerosols or oils. For topical administration to the skin, mouth, eye or other external tissues a topical ointment or cream is preferably used. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water base or a water-in-oil base. Pharmaceutical compositions adapted for topical administration to the eye include eye drops. Here the active ingredient can be dissolved or suspended in a suitable carrier, e.g. in an aqueous solvent. Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouthwashes.

(iv) Rectal Administration

Pharmaceutical compositions adapted for rectal administration may be provided as suppositories or enemas.

(v) Nasal Administration

This includes not only administration to the nasal cavity, but also administration via the nasal cavity to another location, e.g. to the lungs.

Pharmaceutical compositions adapted for nasal administration may use solid carriers, e.g. powders (preferably having a particle size in the range of 20 to 500 microns). Powders can be administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nose from a container of powder held close to the nose. Compositions adopted for nasal administration may alternatively use liquid carriers, e.g. include nasal sprays or nasal drops. These may comprise aqueous or oil solutions of the active ingredient.

Compositions for administration by inhalation may be supplied in specially adapted devices, e.g. in pressurised aerosols, nebulizers or insufflators. These devices can be constructed so as to provide predetermined dosages of the active ingredient.

(vi) Vaginal Administration

Pharmaceutical compositions adapted for vaginal administration may be provided as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

(vii) *Parenteral Administration*

- Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injectable solutions or suspensions. These may contain
- 5 antioxidants, buffers, bacteriostats and solutes that render the compositions substantially isotonic with the blood of an intended recipient. Other components that may be present in such compositions include water, alcohols, polyols, glycerine and vegetable oils, for example. Compositions adapted for parenteral
- 10 administration may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, e.g. sterile water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.
- 15 From the above description it will be appreciated that compositions of the present invention can be formulated in many different way.

Dosages

- 20 Dosages of a compound of the present invention can vary between wide limits, depending upon the nature of the treatment, the age and condition of the individual to be treated, etc. and physician will ultimately determine appropriate dosages to be used.
- 25 However, without being bound by any particular dosages, a daily dosage of a compound of the present invention of from 10 μ g to 100mg/kg body weight may be suitable.

- More preferably the dosage is from 5 to 50mg/kg body weight/day. The dosage
- 30 may be repeated as often as appropriate. If side effects develop, the amount and/or frequency of the dosage can be reduced, in accordance with good clinical practice.

Research Uses

Compounds of the present invention are useful in research. For example, they can be used as research tools for the analysis of one or more of the following: HSF, NF- κ B, the heat shock response, viral replication, viral-mediated disorders, bacterial-mediated disorders, disorders mediated by radiation (e.g. by UV-radiation), inflammatory disorders, disorders of the immune system, ischemia, arteriosclerosis, disorders involving cell proliferation (e.g. cancers), disorders involving damage to, or killing of cells (e.g. oxidative cell damage), and diabetes.

Other Uses

Compounds of the present invention can also be useful in treating plant viral disorders. Given that the basic mechanism of the heat shock response are believed to operate in a similar fashion in plants and animals and that it is reasonable to expect that direct antiviral effects will be produced by the compounds of invention in a similar fashion in plants and animals, the use of compounds of the present invention in treating viral infections of plants is within the scope of the present invention. These infections include, but are not limited to, infections by plants of geminiviruses, rhabdoviruses, caulimoviruses, bromoviruses, tobamoviruses, potyviruses and potexviruses. The use of compounds of the present invention in treating infections by viroids (including, but not limited to, potato spindle tumour viroid, hop stunt viroid, and coconut cadang-cadang viroid) is also within the scope of the invention.

Compounds of the present invention may be particularly useful in treating viral and other disorders affecting aquatic organisms (e.g. fish, crustaceans, etc.). Such disorders include disorders mediated by the snout ulcer virus, iridovirus, lymphocystis disease virus, infectious salmon anaemia, nodaviruses etc.

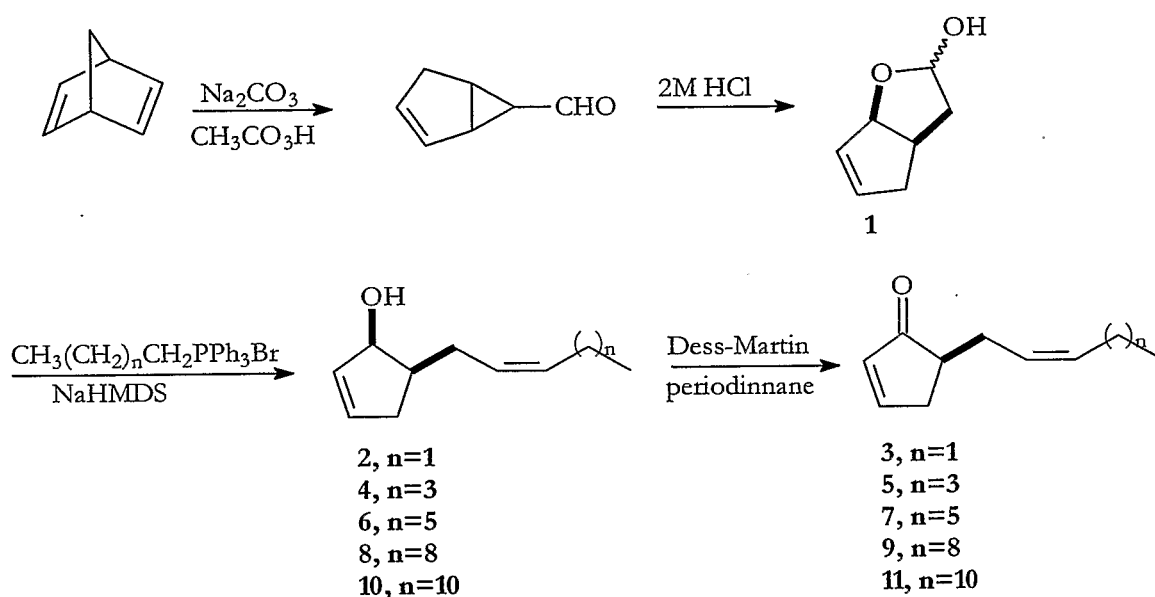
Compounds of the present invention may therefore be used in aquaculture. They may be used in food for aquatic organisms. Such food is within the scope of the present invention. It will generally be sold in sealed containers and labelled appropriately (e.g. as fish food, food for crustaceans, food for aquatic organisms,

etc.). Alternatively, compounds of the present invention may be used for water treatment or for direct application to aquatic organisms. Such compounds do not therefore need to be present in foodstuffs in order to be useful in aquaculture.

5

Examples

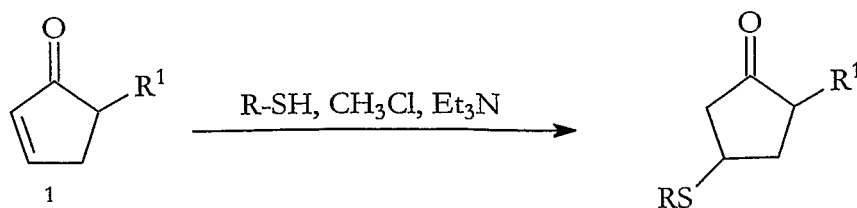
Compounds of formula I in accordance with the invention can be prepared by the following general method (general method A).



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Compounds of formula II can be prepared from the equivalent compounds of formula I using the following general method (general method B).

15

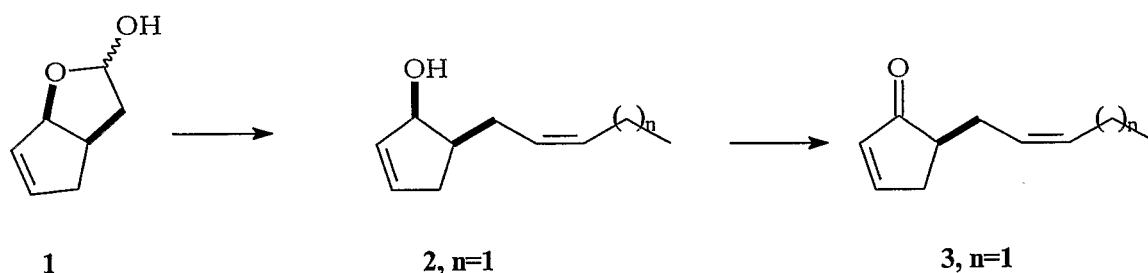


20

General Procedure: Add a catalytic amount of triethyl amine (20 μ l) to a solution of the enone (**1**) (0.25 mM) and thiol (0.25-0.275 mM) in dry chloroform (5 ml), at room temperature, and stir the reaction mixture at room temperature for 1-3 days under a nitrogen atmosphere. The chloroform should then be removed under vacuum and residue purified by flash column chromatography over silica using ethyl acetate in hexane as eluent to afford the title compound **2**.

Example 1

Preparation of ((Z)-5-Pent-2-enyl)-cyclopent-2-enone (3) (CTC-73)



A solution of sodium bis(trimethylsilyl)amide in THF (2.40 ml, 1.0 mol dm⁻³, 2.40 mmol) was added dropwise over 10 minutes to a stirred solution of propyltriphenylphosphonium bromide (1.16 g, 3.01 mmol) in THF (5 ml) at room temperature, under an atmosphere of nitrogen. The solution was stirred at room temperature for 30 minutes and a solution of the previously described lactol **1** (152 mg, 1.20 mmol) in THF (5 ml) was then added *via* cannula over 20 minutes. The mixture was then stirred at room temperature for 17 hours and ammonium chloride (sat'd. aq., 10 ml) was added slowly. The resulting mixture was then extracted with ethyl acetate (3 x 20 ml) and the combined extracts were dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography (SiO₂, 30 % diethyl ether in hexane) gave the alkene **2** (112 mg, 0.74 mmol, 61 %) as a light yellow oil which was immediately taken on.

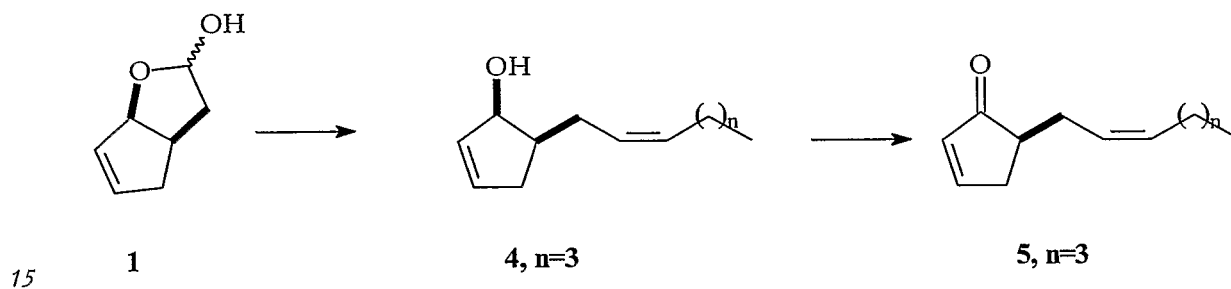
Dess-Martin periodinnane (440 mg, 1.04 mmol) was added in one portion to a stirred solution of the allylic alcohol **2** (105 mg, 0.69 mmol) in dichloromethane (14

ml) at 0 °C, under an atmosphere of nitrogen. The mixture stirred at 0 °C for an hour, then evaporated *in vacuo*. Flash chromatography (SiO₂, 25 % diethyl ether in petrol) gave the cyclopentenone **3** (88 mg, 0.59 mmol, 85 %) as a pale yellow oil;

5 δ_H (400 MHz, CDCl₃) 7.68 (1H, dt *J* 5.7 & 2.8Hz, CH=CHC=O), 6.19 (1H, dt *J* 5.7 & 2.1Hz, CH=CHC=O), 5.51-5.42 (1H, m, CH=CH), 5.30-5.22 (1H, m, CH=CH), 2.82 (1H, ddt *J* 19.6, 6.9 & 2.5Hz), 2.56-2.47 (1H, m), 2.42-2.32 (2H, m), 2.24-2.14 (1H, m), 2.11-1.94 (2H, m), 0.95 (3H, t *J* 7.6Hz, CH₂CH₃); δ_C (100 MHz, CDCl₃) 211.9 (s), 163.7 (d), 134.0 (d), 133.9 (d), 125.0 (d), 44.6 (d), 34.9 (t), 28.4 (t), 20.6 (t),
10 14.2 (q).

Example 2

Preparation of ((*Z*)-5-Hept-2-enyl)-cyclopent-2-enone (**5**) (CTC-74)



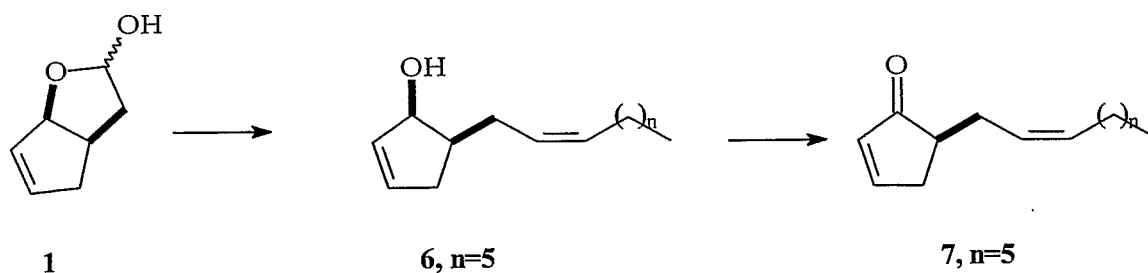
A solution of sodium bis(trimethylsilyl)amide in THF (2.20 ml, 2.0 mol dm⁻³, 4.40 mmol) was added dropwise over 15 minutes to a stirred solution of
20 pentyltriphenylphosphonium bromide (2.25 g, 5.44 mmol) in THF (10 ml) at room temperature, under an atmosphere of nitrogen. The solution was stirred at room temperature for 30 minutes and a solution of the previously described lactol **1** (275 mg, 2.18 mmol) in THF (10 ml) was then added *via* cannula over 15 minutes. The mixture was then stirred at room temperature for 64 hours and ammonium chloride
25 (sat'd. aq., 20 ml) was added slowly. The resulting mixture was then extracted with ethyl acetate (4 x 20 ml) and the combined extracts were dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography (SiO₂, 25 % diethyl ether in hexane) gave the alkene **4** (245 mg, 1.36 mmol, 62 %) as a yellow oil which was immediately taken on.

A solution of Dess-Martin periodinane in dichloromethane (4.5 ml, 15 %w/v, 1.59 mmol) was added in one portion to a stirred solution of the allylic alcohol **4** (240 mg, 1.33 mmol) in dichloromethane (20 ml) at 0 °C, under an atmosphere of nitrogen. The mixture stirred at 0 °C for 45 minutes, then evaporated *in vacuo*. Flash chromatography (SiO₂, 20 % diethyl ether in petrol) gave the cyclopentenone **5** (164 mg, 0.92 mmol, 69 %) as a pale yellow oil;

δ_{H} (400 MHz, CDCl₃) 7.69 (1H, dt J 5.6 & 2.8 Hz, CH=CHC=O), 6.20 (1H, dt J 5.6 & 2.1 Hz, CH=CHC=O), 5.51-5.43 (1H, m, CH=CH), 5.34-5.25 (1H, m, CH=CH), 2.82 (1H, ddt J 19.5, 6.7 & 2.4 Hz), 2.58-2.49 (1H, m), 2.43-2.33 (2H, m), 2.24-2.16 (1H, m), 2.08-2.00 (2H, m), 1.35-1.29 (4H, m, CH₂CH₂CH₃), 0.92-0.87 (3H, m, CH₂CH₃); δ_{C} (100 MHz, CDCl₃) 211.9 (s), 163.7 (d), 133.9 (d), 132.4 (d), 125.5 (d), 44.6 (d), 34.9 (t), 31.8 (t), 28.5 (t), 27.0 (t), 22.3 (t), 13.9 (q).

Example 3

Preparation of ((*Z*)-5-Non-2-enyl)-cyclopent-2-enone (**7**) (CTC-83)



A solution of sodium bis(trimethylsilyl)amide in THF (1.60 ml, 2.0 mol dm⁻³, 3.20 mmol) was added dropwise over 12 minutes to a stirred solution of heptyltriphenylphosphonium bromide (1.75 g, 3.96 mmol) in THF (8 ml) at room temperature, under an atmosphere of nitrogen. The solution was stirred at room temperature for 45 minutes and a solution of the previously described lactol **1** (200 mg, 1.59 mmol) in THF (8 ml) was then added *via* cannula over 10 minutes. The mixture was then stirred at room temperature for 64 hours and ammonium chloride (sat'd. aq., 15 ml) was added slowly. The resulting mixture was then extracted with

ethyl acetate (4 x 15 ml) and the combined extracts were dried over MgSO_4 and evaporated *in vacuo*. Flash chromatography (SiO_2 , 20 % diethyl ether in hexane) gave the alkene **6** (258 mg, 1.24 mmol, 78 %) as a light orange oil which was immediately taken on.

5

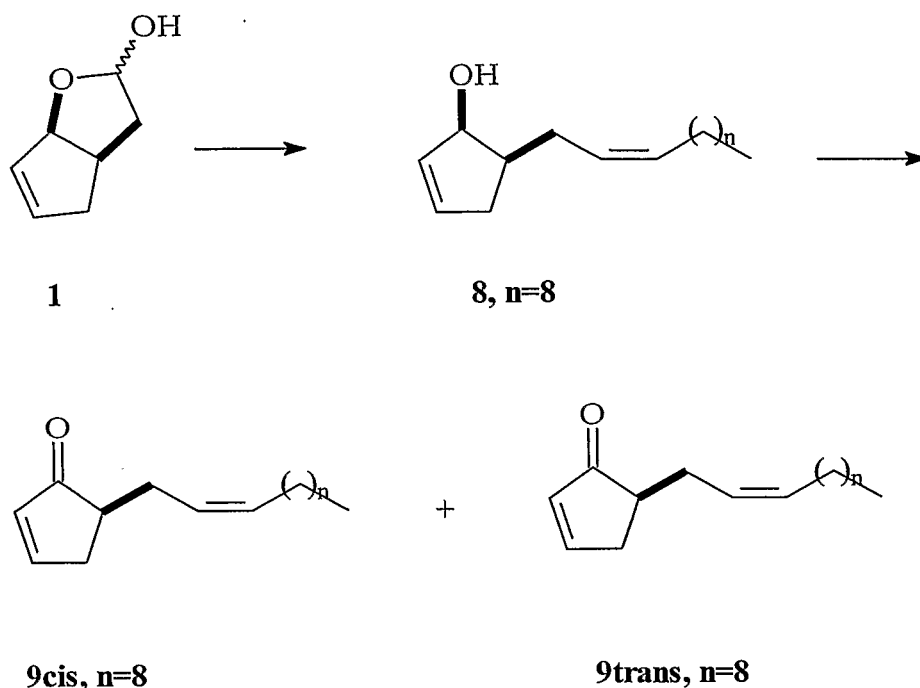
A solution of Dess-Martin periodinane in dichloromethane (4.2 ml, 15 %w/v, 1.49 mmol) was added in one portion to a stirred solution of the allylic alcohol **6** (255 mg, 1.22 mmol) in dichloromethane (20 ml) at 0 °C, under an atmosphere of nitrogen. The mixture stirred at 0 °C for 2 hours, then evaporated *in vacuo*. Flash
10 chromatography (SiO_2 , 15 % diethyl ether in petrol) gave the cyclopentenone **7** (217 mg, 1.05 mmol, 86 %) as a light yellow oil;

δ_{H} (400 MHz, CDCl_3) 7.68 (1H, dt J 5.7 & 2.8Hz, $\text{CH}=\text{CHC}=\text{O}$), 6.19 (1H, dt J 5.7 & 2.0Hz, $\text{CH}=\text{CHC}=\text{O}$), 5.52-5.43 (1H, m, $\text{CH}=\text{CH}$), 5.33-5.25 (1H, m, $\text{CH}=\text{CH}$),
15 2.82 (1H, ddt J 19.5, 6.8 & 2.4Hz), 2.57-2.49 (1H, m), 2.42-2.33 (2H, m), 2.24-2.13 (1H, m), 2.07-2.00 (2H, m), 1.35-1.24 (8H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88 (3H, t J 6.9Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 211.8 (s), 163.5 (d), 133.9 (d), 132.5 (d), 125.6 (d), 44.7 (d), 35.0 (t), 31.7 (t), 29.6 (t), 29.0 (t), 28.5 (t), 27.3 (t), 22.6 (t), 14.0 (q).

20

Example 4

Preparation of ((*Z*)-5-Dodec-2-enyl)-cyclopent-2-enone (**9cis**) (CTC-84) and ((*E*)-5-Dodec-2-enyl)-cyclopent-2-enone (**9trans**) (CTC-85)



A solution of sodium bis(trimethylsilyl)amide in THF (1.60 ml, 2.0 mol dm⁻³, 3.20 mmol) was added dropwise over 15 minutes to a stirred solution of
 5 decyltriphenylphosphonium bromide (1.92 g, 3.97 mmol) in THF (8 ml) at room temperature, under an atmosphere of nitrogen. The solution was stirred at room temperature for 45 minutes and a solution of the previously described lactol **1** (200 mg, 1.59 mmol) in THF (8 ml) was then added *via* cannula over 10 minutes. The mixture was then stirred at room temperature for 68 hours and ammonium chloride
 10 (sat'd. aq., 15 ml) was added slowly. The resulting mixture was then extracted with ethyl acetate (4 x 15 ml) and the combined extracts were dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography (SiO₂, 20 % diethyl ether in hexane) gave the alkene **8** (301 mg, 1.20 mmol, 76 %) as a light yellow oil which was immediately taken on.

15 A solution of Dess-Martin periodinane in dichloromethane (4.1 ml, 15 %w/v, 1.45 mmol) was added in one portion to a stirred solution of the allylic alcohol **8** (300 mg, 1.20 mmol) in dichloromethane (20 ml) at 0 °C, under an atmosphere of nitrogen. The mixture stirred at 0 °C for 2 hours, then evaporated *in vacuo*. Flash
 20 chromatography (SiO₂, 15 % diethyl ether in petrol) gave the major (*Z*)-cyclopentenone **9cis** (184 mg, 0.74 mmol, 62 %) as a light yellow oil;

δ_{H} (400 MHz, CDCl_3) 7.68 (1H, dt J 5.6 & 2.7Hz, $\text{CH}=\text{CHC}=\text{O}$), 6.19 (1H, dt J 5.6 & 2.0Hz, $\text{CH}=\text{CHC}=\text{O}$), 5.51-5.43 (1H, m, $\text{CH}=\text{CH}$), 5.33-5.25 (1H, m, $\text{CH}=\text{CH}$), 2.82 (1H, ddt J 19.6, 6.8 & 4.7Hz), 2.57-2.49 (1H, m), 2.42-2.33 (2H, m), 2.23-2.14 (1H, m), 2.04 (2H, app. q J 6.7Hz), 1.32-1.25 (14H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (3H, t J 6.8Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 211.8 (s), 163.5 (d), 133.9 (d), 132.5 (d), 125.6 (d), 44.7 (d), 35.0 (t), 31.9 (t), 29.63 (t), 29.57 (t), 29.53 (t), 29.3 (t), 28.5 (t), 27.3 (t), 22.7 (t), 14.1 (q);

and the minor (*E*)-cyclopentenone **9trans** (32 mg, 0.13 mmol, 11 %) as a colourless oil;

δ_{H} (400 MHz, CDCl_3) 7.63 (1H, dd J 5.6 & 2.5Hz, $\text{CH}=\text{CHC}=\text{O}$), 6.17 (1H, dd J 5.6 & 1.9Hz, $\text{CH}=\text{CHC}=\text{O}$), 5.56-5.45 (1H, m, $\text{CH}=\text{CH}$), 5.39-5.31 (1H, m, $\text{CH}=\text{CH}$), 3.04-2.97 (1H, m), 2.52 (1H, dd J 18.8 & 6.4Hz), 2.35-2.15 (2H, m), 2.07-1.98 (3H, m), 1.32-1.24 (14H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (3H, t J 6.8Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 209.7 (s), 167.9 (d), 134.1 (d), 132.9 (d), 125.4 (d), 41.5 (d), 40.5 (t), 32.0 (t), 31.9 (t), 29.55 (t), 29.49 (t), 29.3 (t), 27.4 (t), 22.6 (t), 14.0 (q).

Example 5

Compounds CTC-73a, CTC-74a, CTC-83a, CTC-84a and CTC-85a were prepared from compounds CTC-73, CTC-74, CTC-83, CTC-84 and CTC-85, prepared by the methods described in Examples 1-4, by general method B.

Activity of compounds in accordance with the invention

Preferred compounds of the present invention have activity in one or more of the assays described in Examples 6 and 7 below.

Example 6**Effect of inventive compounds on the reactivity of transcription factors HSF and NF- κ B**

Methods: Human lymphoblastoid Jurkat T cells were grown at 37°C in a 5% CO₂ atmosphere in RPM1 1640 medium (GIBCO BRL, Gaithersburg, MD) supplemented with 10% fetal calf serum (FCS, Hyclone Europe Ltd, UK) 2mM glutamine and antibiotics according to the method described by A. Rossi *et al.* (Proc. Natl. Acad. Sci. USA 94: 746 – 750, 1997). The test compounds were stored as a 100% ethanolic stock solution (100 mM) or in DMSO (100mM) and diluted to the appropriate concentration in culture medium at the time of use. Cells were treated with different concentrations of test compound for 1 hour and then stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA, 25 ng/ml), which is a strong inducer of NF- κ B. Control cells received an equal amount of control diluent. After 3 hours whole-cell extracts were prepared and subjected to analysis of DNA-binding activity by EMSA (Electrophoretic Mobility Shift Assay) for detection of HSF or NF- κ B activation, according to the method described by A. Rossi *et al.* (Proc. Natl. Acad. Sci. USA 94: 746 – 750, 1997).

Specificity of protein-DNA complexes was verified by immunoreactivity with polyclonal antibodies specific for p65 (Rel A) or for HSF-1, for NF- κ B and HSF respectively. Quantitative evaluation of NF- κ B- and HSF-DNA complex formation was determined by Molecular Dynamics PhosphorImager (MDP) analysis and was expressed in arbitrary units, as described in A. Rossi *et al.* (J. Biol. Chem. 273: 16446 – 16452, 1998). The results from representative experiments are shown for CTC-73, 74, 83, 84 and 85 (as identified above) in figures 1b, 2b, 3b, 4b and 5b, respectively.

Example 7**Effect of inventive compounds on the replication of Sendai Virus**

Methods: Monkey kidney 37RC cells were grown at 37°C under the conditions described in Example 6 for T cells. The parainfluenza Sendai virus (SV) was grown in the allantoic cavity of 10-day-old embryonated eggs. Viral titre was expressed in haemagglutinating units (HAU) per ml; haemagglutinin titration was done according

to standard procedures using human 0 Rh+ erythrocytes, as described in C. Amici *et al.* (J. Virol. 68: 6890 – 6899, 1994). Confluent monolayers of 37RC cells were infected with SV virus (5 HAU/10⁵ cells) for 1 h at 37°C, and then treated with different concentrations of test compounds. Virus yield at 24 hours after infection
5 was determined in the supernatant of infected cells by HAU titration. The results from representative experiments are shown for CTC-73, 74, 83, 84 and 85 (as identified above) in figures 1a, 2a, 3a, 4a and 5a, respectively. These results show that all of these latter compounds are potent inhibitors of Sendai virus replication.

10 The ID₅₀ (the 50% inhibitory dose/concentration) values at 24hours for the tested compounds are given below.

	<i>Compound</i>	<i>ID₅₀ / μM</i>
	CTC-73	7
15	CTC-74	1
	CTC-83	10
	CTC-84	7
	CTC-85	10

20 **Example 8**

MTT assay

Cell viability can be determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Uninfected A549 (7.5 x 10⁴ cells/well in 96 well plates) or 37RC cells (2.5 x 10⁴ cells/well in 96 well plates) are treated with
25 different concentrations of inventive compound or ethanol diluent for 24 hours. After this time, 10 ml of a 0.5% MTT solution in PBS is added to the monolayers and the mixture is incubated for 2 h at 37°C. Reduced MTT (formazan) is extracted from cells by adding 100 μl of acidic isopropanol containing 10% Triton X-100, and formazan absorbance is measured in an ELISA microplate reader at two different
30 wavelengths (540 and 690 nm).

General Remarks

The foregoing description of the invention is merely illustrative thereof and it should therefore be appreciated that various variations and modifications can be made without departing from the spirit or scope of the invention as set forth in the
5 accompanying claims.

Where preferred or optional features are described in connection with particular aspects of the present invention, they shall be deemed to apply *mutatis mutandis* to other aspects of the invention unless the context indicates otherwise.

10

All documents cited herein are hereby incorporated by reference, as are any citations referred to in said documents.

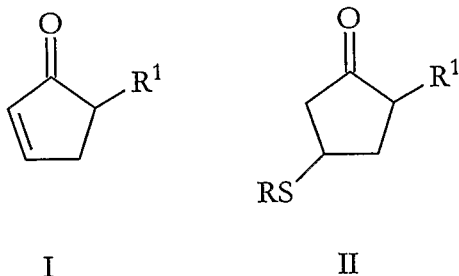
References

1. Feige U, Morimoto R, Yahara I, Polia BS. *Stress-inducible Cellular Responses*. Birkhäuser Verlag, Basel Boston Berlin, 1996.
- 5 2. Marber MS, Walker JM, Latchman DS, Yellon DM. *J. Clin. Invest.* 93, 1087 – 1094, 1994.
3. Feinstein DL *et al.* *J. Biol. Chem.* 271, 17724 – 17732, 1996.
4. Amici C, Giorgi C, Rossi A, Santoro MG. *J. Virol* 68, 6890 – 6897, 1994.
5. Santoro MG, in *Stress-inducible Cellular Responses*. (Feige U *et al.* eds,
10 Birkhäuser Verlag, Basel Boston Berlin) pp. 337 – 357, 1996.
6. Santoro MG, Garaci G, Amici C. *P.N.A.S. USA* 86, 8407 – 8411, 1989.
7. Amici C, Sistonen L, Santoro MG, Morimoto RI. *P.N.A.S. USA* 89, 6227-6231, 1992.
8. Santoro MG, Benedetto A, Carruba G, Garaci E, Jaffe B. *Science* 209, 1032 –
15 1034, 1980.
9. Santoro MG, *Trends Microbiol.* 5, 276 – 281, 1997.
10. Rozera C, Carattoli A, De Marco A, Amici C, Giorgi C, Santoro MG *J. Clin. Invest.* 97; 1795 – 1803, 1996.
11. Rossi A, Elia G, Santoro MG. *P.N.A.S. USA* 94, 746 – 750, 1997.
- 20 12. Thanos D, Maniatis T. *Cell* 80, 529-532, 1995.
13. Rossi A, Elia G, Santoro MG. *J. Biol. Chem.* 271, 32192-32196, 1996.
14. Shield MJ. *Pharmacol. Ther.* 65, 125 – 137, 1995.
15. Sinclair SB *et al.* *J. Clin. Invest.* 84, 1063 – 1067, 1989.
16. Baeuerle PA and Henkel T (1994). Function and Activation of NF-Kappa B
25 in the Immune System. *Annual Reviews of Immunology* 12: 141 – 179.
17. Colville-Nash PR *et al.* (1998). Inhibition of Inducible Nitric Oxide Synthase by Peroxisome Proliferator-Activated Receptor Agonists: Correlation with Induction of Heme Oxygenase 1. *Journal of Immunology* 161, 978 – 984.
18. K. J. Stone, R. D. Little, *JOC*, 1984, 49, 1849-1853.
- 30 19. A. Kawamoto, H. Kosugi, H. Uda, *Chem. Lett.*, 1972, 807-810.
20. Moriguchi I, Hirono S, Liu Q, Nakagome Y, and Matsushita Y, (1992) Simple method of calculating octanol/water partition coefficient. *Chem. Pharm. Bull.* 40, 127 –130.

21. Lipinski C, Lombardo F, Dominy B, Feeney P, (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews* 23 (1997) 3 –25.
- 5 22. Kondo, M.; Oya-Ito, T.; Kumagai, T.; Osawa, T.; Uchida, K. *J. Biolog. Chem.* 2001, 276, 12076-12083.
23. Silverman, R. B., In *The Organic Chemistry of Drug Design and Drug Action*; Academic Press; A Harcourt Science and Technology Company: San Diego, 1992, 336-338.
- 10 24. R. J. Flanagan, *Chemistry in Britain*, 2002, 28.
25. Meister, A., Anderson, M., E., *Ann. Rev. Biochem.* 1983, 52, 711-760.

Claims

1. A compound of formula I or II: -



wherein:

R is a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, or aralkynyl group, that optionally includes at least one heteroatom in its carbon skeleton; and,

- R¹ is a substituted or unsubstituted, branched or straight chain alkyl, alkenyl, or alkynyl group, that contains 1-12 carbon atoms.

2. A compound as claimed in claim 1, wherein R is an R²CH₂ group, wherein R² is a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, or aralkynyl group, that optionally includes at least one heteroatom in its carbon skeleton.

3. A compound as claimed in claim 1 or claim 2, wherein R contains 1-12 carbon atoms.

4. A compound as claimed in any of the preceding claims, wherein R includes at least one hydrophilic group.

5. A compound as claimed in claim 4, wherein said hydrophilic group is or includes a hydroxyl, carbonyl, carboxyl, amino, amido, quaternary ammonium or thiolyl group.

6. A compound as claimed in claim 5, wherein R provides the functionality of an amine, amide, peptide, ester, carboxylic acid, carboxylic acid salt, alcohol, aldehyde, ketone or thiol.

5 7. A compound as claimed in any of the preceding claims, wherein the group –SR is an S-cysteinyl or a substituted S-cysteinyl group.

8. A compound as claimed in claim 7, wherein the substituted S-cysteinyl group is a di- or tri-peptide group that includes an S-cysteinyl moiety.

10

9. A compound as claimed in claim 8, wherein the substituted S-cysteinyl group is an S-glutathionyl, S-cysteinyl, N-tert-butoxycarbonyl S-cysteinyl or N-tert-butoxycarbonyl S-cysteinyl ester group.

15 10. A compound as claimed in any preceding claim, wherein R¹ includes up to 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms.

11. A compound as claimed in any preceding claim, wherein R¹ includes at least 4 carbon atoms.

20

12. A compound as claimed in any preceding claim, wherein R¹ is unsubstituted.

13. A compound as claimed in any preceding claim, wherein R¹ is unbranched.

25 14. A compound as claimed in any preceding claim, wherein R¹ is unsaturated.

15. A compound as claimed in any preceding claim, wherein R¹ is an alkenyl group.

30 16. A compound as claimed in claim 15, wherein R¹ comprises an unbranched carbon chain extending from the cyclopentenone ring in formula I, or the cyclopentanone ring in formula II, that includes a single double bond located

between the second and third carbon atoms from the cyclopentenone ring in formula I, or the cyclopentanone ring in formula II.

17. A compound as claimed in claim 16, wherein the unbranched carbon chain is
5 in the cis- or (Z) form.
18. A compound as claimed in any preceding claim, wherein R¹ includes 5, 7, or 12 carbon atoms.
- 10 19. A compound as claimed in any preceding claim, wherein R¹ is -CH₂ CH=CH (CH₂)_n CH₃, and n is 0-8.
20. A compound as claimed in claim 19, wherein n is 1, 2, 3, 4, 5, 6, 7, or 8 and, preferably, 1, 3 or 8.
- 15 21. A compound of formula II, as claimed in any preceding claim, having a calculated or measured logP value that is at least 0.25, 0.5, 0.75, 1 or 1.25 lower than the logP value for the equivalent compound of formula I, wherein the logP values for said compounds are calculated or measured using the same technique.
- 20 22. A compound as claimed in any preceding claim, that is pharmaceutically, or therapeutically active.
23. A compound as claimed in any preceding claim for use in medicine.
- 25 24. A compound as claimed in any preceding claim, for treating the human or animal body by therapy, or for use in a diagnostic method practiced upon the human or animal body.
- 30 25. A compound as claimed in any of the preceding claims having activity in respect of one or more of the following:

- a) activating HSF
- b) inhibiting NF- κB

- c) inhibiting the replication of HSV-1
- d) inhibiting the replication of Sendai virus.

26. A compound as claimed in any of claims 22-25, for treating a viral-mediated
5 disorder, a bacterial-mediated disorder, a disorder mediated by radiation, an
inflammatory disorder, a disorder of the immune system, ischemia, arteriosclerosis,
a disorder involving cell proliferation, a disorder involving damage to cells or killing
of cells, diabetes, a disorder affecting an aquatic organism, oxidative stress, a
degenerative disease, burns or a disorder involving calcium loss or deficiency, or for
10 use as an anti-oxidant, in combating the effects of ageing, or in promoting wound
healing.

27. A compound as claimed in claim 26, wherein the disorder involving cell
proliferation is a cancer.

15

28. A compound as claimed in claim 26, wherein the degenerative disease is
neuro-degenerative disease, optionally BSE, new variant CJD, or Alzheimer's
disease.

29. Use of a compound as claimed in any of claims 1 to 22 as a research tool for
the analysis of one or more of the following: HSF, NF- κ B, the heat shock response,
viral replication, viral-mediated disorders, bacterial-mediated disorders, disorders
mediated by radiation, inflammatory disorders, disorders of the immune system,
ischemia, arteriosclerosis, disorders involving cell proliferation, disorders involving
25 damage to, or killing of cells, or diabetes.

30. A pharmaceutical composition comprising a compound according to any of
claims 1-28 and optionally including a pharmaceutically acceptable carrier.

31. A composition as claimed in claim 30 for use in medicine, preferably for
treating a disorder as recited in any one of claims 26-28.

30

32. A food for an aquatic organism comprising a compound according to any of claims 1-22.

33. An aquatic environment comprising a compound according to any of claims
5 1-22.

34. Use of a compound as claimed in any of claims 1-28 for the manufacture of a medicament for use in a therapeutic or diagnostic method practiced on the human or animal body.

10

35. A use as claimed in claim 34, for the preparation of a medicament for treating a viral-mediated disorder, a bacterial-mediated disorder, a disorder mediated by radiation, an inflammatory disorder, a disorder of the immune system, ischemia, arteriosclerosis, a disorder involving cell proliferation, cancer, a disorder involving
15 damage to cells or killing of cells, diabetes, oxidative stress, a degenerative disease, burns, a disorder involving calcium loss or deficiency, or a disorder effecting an aquatic organism.

36. A use as claimed in claim 34, for the preparation of a medicament for use as
20 an anti-oxidant, in promoting wound healing or use in combating the effects of ageing.

37. A use as claimed in claim 35, for the preparation of a medicament for use in treating a neuro-degenerative disease, preferably BSE, new variant CJD, or
25 Alzheimer's disease.

38. A method for treating a condition, disorder or infection in a human or animal subject, comprising administering a therapeutically effective amount of a compound as claimed in any of claims 1-28 or a composition as claimed in claim 30
30 or 31 to said subject.

39. A method of treating a viral-mediated disorder, a bacterial-mediated disorder, a disorder mediated by radiation, an inflammatory disorder, a disorder of

the immune system, ischemia, arteriosclerosis, a disorder involving cell proliferation, cancer, a disorder involving damage to cells or killing of cells, diabetes, oxidative stress, a degenerative disease, the effects of ageing, burns, a disorder involving calcium loss or deficiency, or a disorder effecting an aquatic
5 organism, comprising administering a compound as claimed in any one of claims 1-28 or a composition as claimed in claim 30 or 31 to a subject suffering from one or more of said conditions, in an amount effective to at least ameliorate at least one of said conditions.

10 40. A method of promoting wound healing, comprising administering a compound as claimed in any one of claims 1-28 or a composition as claimed in claim 30 or 31 to a wounded subject in an amount effective to promote wound healing.

15 41. A method as claimed in claim 39, wherein the degenerative disease is a neuro-degenerative disease, preferably BSE, new variant CJD, or Alzheimer's disease.

42. A method of decreasing the lipophilicity and/or increasing the water
20 solubility and/or the therapeutic index of a pharmaceutically active compound of formula I as defined in any of claims 1-20, said method comprising forming an adduct of said compound of formula I and a thiol of the formula HSR, wherein R is a group as defined in any of claims 1-9 and the adduct is a compound of formula II as defined in any of claims 1-20.

25 43. A method as claimed in claim 42, wherein the adduct is formed via a Michael reaction between the unsaturated compound of formula I and the thiol.

44. An adduct, prepared or preparable by a method as claimed in claim 42 or
30 claim 43.

45. A compound as claimed in any of claims 1-24, that exhibits a capacity to activate HSF at a concentration at which said compound has no significant inhibitory effect on NF- κ B activity.

5 46. A compound as claimed in claim 45, for use in treating a condition responsive to a heat shock response.

47. A compound as claimed in claim 45 or 46, for use in treating a virally mediated disorder.

10

48. A compound as claimed in claim 47, for use in treating a viral infection wherein an inflammatory component is not essential to the pathology of the infecting virus, or wherein a pathological effect of the infecting virus can be reversed or prevented by a heat shock response.

15

49. A compound as claimed in claim 47, for use in treating an infection with a virus that is not dependant upon NF- κ B for replication, or does not have κ B elements in its genome.

20

50. A compound as claimed in claim 45 or 46, for use in a cytoprotective treatment.

51. A compound as claimed in claim 45 or 46, for use in treating a disorder that involves damaging or killing cells.

25

52. Use of a compound as claimed in claim 45 for the manufacture of a medicament for use in a therapeutic or diagnostic method practised on the human or animal body.

30

53. A use as claimed in claim 52, wherein the medicament is for use in a therapeutic treatment as defined in any one of claims 46-51.

54. A method of treating a condition, disorder or infection in a human or animal subject, comprising administering a therapeutically effective amount of a compound as claimed in claim 45 to said subject, wherein said condition, disorder or infection is as defined in any of claims 46-51.

5

55. A method of providing a cytoprotective treatment to a human or animal subject, comprising administering a therapeutically effective amount of a compound as claimed in any of claims 45-51 to said subject.

10 56. A cytoprotective method, comprising administering a cytoprotective amount of a compound as claimed in any of claims 45-51 to a human or animal subject.