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Chemical compounds and their uses

The present invention relates to chemical compounds and their uses. More particularly, the present invention relates to cyclopentenones and to their uses in medicine.

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 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 signal for detection of physiological stress, it is now accepted that HSPs are utilised by the 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 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).

The ability of prostaglandins of the A type (PGAs) to inhibit virus replication and prevent the establishment of persistent infections was first reported in 1980 (8). It is now well established that PG 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).



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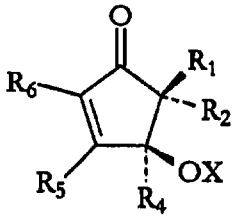
The mechanism of the antiviral activity is distinct from any other known antiviral agent and involves the induction of heat shock proteins and the inhibition of the transcription factor NF-κB (nuclear factor-κB) in the infected cell.

NF-κB is an inducible eukaryotic transcription factor which has a critical role in promoting inflammation and viral replication (11). In most cells NF-κB exists in an inactive cytoplasmic complex, whose predominant form is a heterodimer composed of p50 and p65 subunits, bound to inhibitory proteins of the IκB family, usually IκBα, and is activated in response to primary (viruses, bacteria, UV) or secondary (inflammatory cytokines) pathogenic stimuli (12). Stimulation triggers rapid phosphorylation and degradation of IκBα, resulting in NF-κB translocation to the nucleus, where the factor binds to DNA at specific κB-sites, inducing a variety of genes encoding signalling proteins. Target genes include inflammatory and chemotactic cytokines, cytokine receptors and viral genes. NF-κB 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-κB activation and NF-κB-dependent HIV-1 transcription in human cells, by preventing IκBα phosphorylation and degradation, and that this effect is strictly associated with HSF1 activation (11).

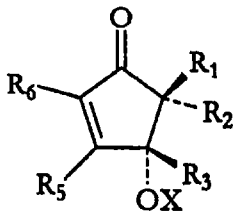
Santoro *et al.* have identified the molecular structure of natural prostaglandins responsible for HSF activation and NF-κB inhibition (13). One component of the PGA molecule, cyclopent-2-en-1-one (also known as 2-cyclopenten-1-one), at a concentration of 125-500μM, has been shown to be able to activate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

The present inventors have now identified compounds that have surprisingly high activity (relative to cyclopent-2-en-1-one) in various assays that are described in Examples 1 to 3.

According to the present invention there is provided a compound for use in medicine with formula (a) or (b):-



(a)



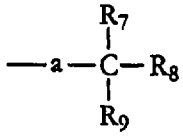
(b)

wherein: R_1 and R_2 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic,

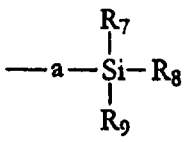
R_3 and R_4 are hydrogen,

R_5 and R_6 are, independently, hydrogen or a halogen,

and X has the formula:-



or



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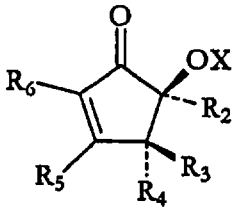
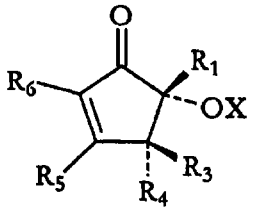
wherein R_7, R_8 and R_9 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic, and "a" is absent or a linking group, optionally a hydrocarbyl linking group;

or with formula (c) or (d):-



(c)



(d)

wherein: R_1 and R_2 are hydrogen,

R_3 and R_4 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic, and

R_5, R_6 and X are as defined above.

Further aspects and embodiments of the invention are defined and described in attached claims 2 – 30.

Where a plurality of carbon atoms are present in any of R_1, R_2, R_3, R_4 it is preferred that between 2 and 20 (more preferably between 3 and 15) carbon atoms are present. R_1, R_2, R_3 and R_4 may comprise cyclic or non-cyclic groups. A functional group (e.g., a carboxylic acid group) may be included.

Preferably however, R_1, R_2, R_3 and R_4 are not halogen.

Desirably a plurality of R_1, R_2, R_3 and R_4, R_5 and R_6 are hydrogen. In some cases all of R_1, R_2, R_3, R_4, R_5 and R_6 may be hydrogen.

R_7, R_8, and R_9, are preferably substituted alkyl, aryl or substituted aryl, "a" can be moiety providing a linkage with the oxygen of –O-X (e.g., it is a hydrocarbyl linker, such as CH_2, C_2H_4 or C_3H_6).

Preferably X is hydrophobic and/or lipophilic. It may, for example, have only 1, 2 or 3 carbon atoms. Desirably, however, it comprises at least 4 carbon atoms. A maximum number of carbon atoms for X has not been determined. However, without being bound by theory, it is envisaged that compounds with up to 50 or up to 20 carbon atoms (more preferably up to 12 carbon atoms and most preferably up to 8 carbon atoms) will normally be used in the present invention.

It is important to note that in order to be effective compounds for use in the present invention do not require the presence of the long aliphatic lateral side chains that are present in those prostaglandins or punaglandins that have a cyclopentenone ring

structure (sometimes referred to as a cyclopentenone nucleus). Thus one or both such side chains may be absent at the 4 and/or 5 positions of the cyclopentenone ring. The known punaglandin derivative shown in Figure 3b) has such a side chain and is expressly disclaimed from the scope of the present invention.

If a side chain is present at positions R_3 and/or R_4 shown in Figure 1, then preferably it has no more than 7 carbon atoms. More preferably it has no more than 3 carbon atoms. However it is most preferred that R_3 and/or R_4 are hydrogen.

From the foregoing description it will be appreciated that compounds of the present invention includes various 4- and 5-oxacyclopent-2-en-1-ones . An oxa moiety (provided by -O-X) may be present at both 4 and 5 positions of the cyclopentenone ring (in either *cis* or *trans* form). The -O-X group may be provided twice at the 4 position and/or at the 5 position, if desired.

Some non-limiting examples of compounds within the scope of the present invention are shown in Figure 10. (R and S, as well as *cis* and *trans* forms are all covered, where applicable, and therefore the stereochemistry should not be construed as limiting):-

For the compounds shown in Figure 10, "A" indicates that one or more additional substituents may optionally be present on the cyclopentenone ring. If present, they are preferably small groups or atoms and desirably do not include more than 7 or more than 3 carbon atoms. However, it is preferred that additional substituents are not present – i.e. that A is absent. "Z" is preferably H or halogen (e.g. chlorine).

In compounds (i) and (ii) shown in Figure 10, "R" is a moiety incorporating up to 8 carbon atoms or a moiety incorporating one or more heteroatoms (preferably at least one Si atom) and up to 50 carbon atoms. R is preferably a hydrocarbyl group that is optionally substituted.

In compound (iii) shown in Figure 10, R^1 and R^2 are such that either:-

a) at least one of R^1 and R^2 incorporates one or more heteroatoms (preferably at least one Si atom) and up to 30 or up to 50 carbon atoms, or

b) at least one of R^1 and R^2 comprises up to 8 carbon atoms.

Preferably at least one of R^1 and R^2 is an optionally substituted hydrocarbyl group. The other of R^1 and R^2 may also be an optionally substituted hydrocarbyl group, but this is not essential. It may for example be hydrogen or another atom or group. R^1 and R^2 may be the same or different.

In compound (iv) shown in Figure 10, X and / or Y may be absent or may be groups or atoms providing a linkage between O and Si. X and / or Y may, for example, be an optionally substituted hydrocarbyl group. For example X and / or Y may be CH_2, C_2H_4, or C_3H_6. X and Y may be the same or different. R^1 and R^2 can be any appropriate moieties and may be the same or different. Preferably however at least one (desirably both) of R^1 and R^2 is a hydrocarbyl group. The hydrocarbyl group may be optionally substituted. The hydrocarbyl group preferably comprises up to 30 or up to 50 carbon atoms.

Preferred compounds for use in the present invention have higher activity than cyclopent-2-en-1-one 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.

Activity can be assayed by following the procedures set out in Example 1 (for a) and

b)), in Example 2 (for c)) or in Example 3 (for d)).

Increased activity relative to cyclopent-2-en-1-one need not exist at all concentrations. It is however preferred that it exists over a range of 1 - 200 μM or over at least part of said range.

Preferably a level of activity can be obtained using compounds of the present invention that is at least twice the level of cyclopent-2-en-1-one. More preferably it is at least 10 times that of cyclopent-2-en-1-one.

Particularly preferred compounds for use in the present invention include the R and S enantiomers of 4-tert-butyldimethylsiloxy-cyclopent-2-en-1-one (see Figures 2a) and 2b) respectively).

Both forms have unexpectedly high levels of activity, being at least 100 times more effective in activating HSF and inhibiting NF-κB than cyclopent-2-en-1-one. It is particularly surprising that the S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one enantiomer is so active, given that this isomeric form does not correspond with the form of prostaglandins that occurs in nature (the R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one form).

In view of these findings, both R- and S-enantiomers of all compounds described in connection with the present invention are considered useful and may each be provided in a form substantially free of the other enantiomer (e.g. at least 75% free (w/w), at least 90% free (w/w) or at least 99% free (w/w)). Mixtures of these enantiomers (e.g. racemic mixtures) may however be used if desired.

Certain findings in respect of the present invention may be explained by a theory referred to as the "anchor theory", which is provided for the first time below. It is however important to note that the present invention does not rely upon this theory

and therefore if it turns out to be incorrect this has no bearing upon the validity of the present invention.

Anchor theory

The active part of prostaglandin molecules that stimulate HSP and inhibit NF-κB is the cyclopentenone ring structure. This is present in two classes of prostaglandins: the PGA series (see Fig 4a) and the PGJ series (see Fig 4b).

In summary, the anchor theory is that *in vivo* the cyclopentenone nucleus is put in place at or in close proximity to the active site of a receptor by a side chain anchoring it to a hydrophobic domain of a receptor. The cyclopentenone nucleus can associate with and dissociate from the active site of the receptor.

The probability of association and/or the duration of association may be higher when a hydrophobic anchor is present. The presence of a side chain at the S-position (see Fig 4c) may provide an improved anchoring effect (see Fig 4d). A similar effect is believed to occur with the Salbutamol derivative Salmeterol, which has a lipophilic "anchoring" side chain that aids binding and increases its effect on the target β-receptors.

In the most preferred compounds of the present invention, O-X is present at the 4 and / or 5 positions of a cyclopent-2-en-1-one ring, wherein X is a silicon containing group (and is preferably also a hydrocarbyl group, optionally including one or more additional functional groups or heteroatoms). Without being bound by theory, the presence of silicon at these positions may contribute to particular hydrophobicity characteristics leading to an improved anchoring effect.

It is important to note that although various cyclopent-2-en-1-ones with side chains comprising siloxy groups are known, these groups are merely provided as protecting

groups. Prior to the present invention there was no indication that such groups could be used to provide surprisingly high activity, as disclosed herein.

A) Medical Uses

Compounds of the present invention may be used for any desired therapeutic purpose. Preferred treatments are human treatments, although veterinary treatments are also within the scope of the present invention. The treatment may be prophylactic or may be in respect of an existing condition.

Treatments are desirably 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-κB.

Various preferred treatments are discussed below. (It should be appreciated that certain disorders - e.g. cancers - may be mediated both 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 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

NF-κB 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. Furthermore, it has now been shown that compounds of the present invention are surprisingly active in reducing the replication of viruses.

Compounds of the present invention are therefore useful in treating viral-mediated disorders. These include disorders mediated by RNA viruses (which may be

single-stranded, negatively polarised RNA viruses), as well as disorders mediated by DNA viruses.

Examples of viral disorders that can be treated using compounds of the present invention include disorders mediated by: retroviruses (e.g. HIV-1), herpes viruses (e.g. HSV-1, CMV, HHV8, HSV-2), paramyxo and orthomyxo viruses (as illustrated by Sendai viruses and including influenza viruses), rhabdoviruses (e.g. vesicular stomatitis virus, rabies viruses), picornaviruses (e.g. rhinoviruses and hepatitis A viruses), hepadnaviruses (e.g. hepatitis B viruses), togaviruses (e.g. rubella viruses), or poxviruses (e.g. molluscum contagiosum virus).

Additional viral disorders that can be treated using compounds of the present invention include: filoviruses (e.g. Ebola virus), bunyaviruses (e.g. hantaviruses), arenaviruses (e.g. lassa fever virus), flaviviruses (e.g. yellow fever and hepatitis C viruses).

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, by the iridovirus, by the lymphocystis disease virus, 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.

Compounds of the present invention may also be useful in treating plant viral disorders. Given that the basic mechanisms 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 of plants by geminiviruses, rhabdoviruses, caulimoviruses, bromoviruses, tobramoviruses, potyviruses and potexviruses. The use of compounds of the present invention in treating infections by viroids (including, but not limited to, potato spindle tuber viroid, hop stunt viroid, and coconut cadang cadang viroid) is also within the scope of the patent invention.

2. *Treatment of bacterial-mediated disorders*

NF-κB is activated in response to bacterial infections.

Compounds of the present invention are useful in treating disorders arising from such infections - e.g. in treating NF-κB 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*).

3. *Treatment of disorders mediated by radiation*

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

Compounds of the present invention are therefore useful in treating disorders mediated by radiation. Such disorders include cell and tissue trauma, cell and tissue ageing and cancer (e.g. skin cancer).

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

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

Compounds of the present invention are 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 can be treated with compounds of the present invention include rheumatoid arthritis, multiple sclerosis, inflammatory disorders of the airways, adult respiratory distress syndrome, pulmonary hypertension, hepatitis and/or cirrhosis, vascular inflammation (including lupus erythematosis disseminata), and inflammatory disorders of the gastro-intestinal tract (e.g. ulcers).

5. Treatment of Ischemia and Arteriosclerosis

NF-κB has been implicated in the pathogenesis of ischemia and arteriosclerosis.

Compounds of the present invention are therefore useful in treating such disorders. These disorders include reperfusion damage (e.g. in the heart and/or brain) and cardiac hypertrophy.

6. Treatment of disorders involving cell proliferation

NF-κB is implicated in cell proliferation.

Compounds of the present invention are 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).

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

Heat shock proteins are known to provide a cytoprotective effect.

Compounds of the present invention are therefore useful in treating 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 damage, cell and tissue ageing, trauma, hepatitis and diabetes.

8. Other treatments

Cyclopentenone prostaglandins are of known utility in stimulating peroxisome proliferator activated receptors (PPARs). This is a further indication of the utility of compounds of the present invention in treating diabetes (including complications arising therefrom).

Compounds of the present invention can 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.).

A compound of the present invention may be used in the manufacture of a medicament for one or more of the previously mentioned treatments.

A medicament will usually be supplied as part of a pharmaceutical composition, 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 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 (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.

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 (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 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 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 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. 4704355.

Routes of Administration

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 method known in the art of pharmacy, for example by admixing one or more active ingredients with a suitable carrier.

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 by Illum and Davis (Current Opinions in Biotechnology **2,** 254 – 259 (1991)). Different routes of administration for drug delivery will now be considered in greater detail:

(i) Oral Administration

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, 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 with a material that delays disintegration 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 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

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).)

(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 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 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.

From the above description it will be appreciated that compositions of the present invention can be formulated in many different ways. However preferred compositions of the present invention are in the form of topical formulations.

Dosages

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 a physician will ultimately determine appropriate dosages to be used.

However, without being bound by any particular dosages, a daily dosage of a compound of the present invention of from 10μg to 100mg/kg body weight may be suitable.

More preferably the dosage is from 5 to 50 mg/kg body weight/day. The dosage 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.

D) 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-κB, 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.

Novel Compounds

As will be appreciated from the foregoing description, compounds of the present invention have a variety of different uses. It is however important to note that certain compounds are believed to be novel and are therefore covered *per se*.

Such compounds include novel compounds within the scope of the formulae shown in Figure 10. The two compounds shown in Figure 2 are known and are therefore expressly excluded from the scope of novel compounds of the present invention. (However, for the avoidance of doubt it should be noted that pharmaceutical compositions comprising the compounds shown in Figure 2, as well as uses thereof, including medical uses, are included within the scope of the present invention.)

The present invention will now be described by way of example only, with reference to the accompanying drawings, wherein:

Figures 1a) to d) provide the structures of compounds of the present invention.

Figures 2a) and 2b) provide the structures of R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one and S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one respectively (referred to herein as CTC7 and CTC8 respectively).

Figure 3a) provides the structure of cyclopent-2-en-1-one (referred to herein as CTC1).

Figure 3b) provides the structure of a punaglandin derivative disclosed in Japanese patent application number JP6205928.

Figure 4a) provides the structure of PGA_2.

Figure 4b) provides the structure of PGJ_2.

Figure 4c) illustrates the S position of a side chain of a PGA-like molecule.

Figure 4d) illustrates the anchor theory.

Figure 5 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and cyclopent-2-en-1-one (CTC1) on the activity of transcription factors HSF and NF-κB.

Figure 6a) illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and cyclopent-2-en-1-one (CTC1) on the replication of Herpes simplex virus type 1.

Figure 6b) provides a comparison of the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8) on HSV-1 replications with that of Aciclovir.

Figure 7 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and cyclopent-2-en-1-one (CTC1) on the replication of Sendai virus.

Figure 8 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8) or nitrite formation at submicromolar cencentrations. A comparision with PG-J2 is provided.

Figure 9 illustrates the effect of R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) infusion on the blood pressure of normal Wister rats, CTC8 is compared with the prostaglandin PG-E and with the cyclopentenone prostaglandin PG-A.

Figure 10 shows certain preferred compounds of the present invention (both R- and S- and *cis*- and *trans*-forms are covered and stereochemistry should therefore not be construed as limiting).

Examples

Example 1: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the activity of transcription factors HSF and NF-κB.

Methods: Human lymphoblastoid Jurkat T cells were grown at 37°C in a 5% CO2 atmosphere in RPMI 1640 medium (GIBCO BRL, Gaithersburg, MD) supplemented with 10% fetal calf serum (FCS, Hyclone Europe Ltd, UK), 2 mM glutamine and antibiotics according to the method described by A. Rossi *et al.* (Proc. Natl. Acad. Sci. USA 94: 746-750, 1997). CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) were stored as a 100% ethanolic stock solution (100 mM) and diluted to the appropriate concentration in culture medium at the time of use. Cells were treated with different concentrations of CTC8, CTC7 or CTC1 for 1 hour and then stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA, 25 ng/ml), which is a strong inducer of NF-κB. 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-κB 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-κB and HSF respectively. Quantitative evaluation of NF-κB-and HSF- DNA complex formation was determined by Molecular Dynamics PhosphorImager (MDP) analysis and is expressed in arbitrary units, as described in A. Rossi *et al.* (J. Biol. Chem. 273: 16446-16452, 1998). Results from a representative experiment are shown. Each experiment was repeated at least 3 times.

Results and conclusions: The results shown in Fig. 5 indicate that CTC8 and CTC7 are potent inducers of HSF and inhibitors of NF-κB, with CTC8 being more active than CTC7. Both compounds are shown to be at least 100 times more effective in activating HSF and inhibiting NF-κB than the originally described compound cyclopent-2-en-1-one (CTC1).

Example 2: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the replication of Herpes simplex virus type 1.

Methods: Human HEp-2 laryngeal carcinoma cells and monkey VERO cells were grown at 37°C under the conditions described in Example 1 for T cells. Cell viability was determined by dye exclusion technique or by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, Sigma Chemical Co.) to MTT formazan conversion assay, as described by F. Denizot and R. Lang (J. Immunol. Methods 89: 271-277, 1986). Herpes simplex virus type 1 (HSV-1), strain F grown in VERO cells, was used at a multiplicity of infection of 10 plaque forming units (PFU) per cell. Confluent HEp-2 cell monolayers were infected with HSV-1 for 1 h at 37°C. After this time, virus inocula were removed and cells were incubated in RPMI 1640 medium containing 2% FCS. Different concentrations of CTC8, CTC7 or cyclopent-2-en-1-one (CTC1) were added to the culture after the 1 h adsorption period, and maintained in the medium for the duration of the experiment. Control medium contained the same concentration of ethanol diluent, which did not affect cell metabolism or virus replication. HSV-1 virus titres were determined 24 hours after infection by cytopathic effect 50% (CPE50%) assay on confluent VERO cells monolayers in 96-well tissue culture plates (six dilutions for each sample, eight wells for each dilution), as described by F. Pica *et al.* (Antiviral Res. 20: 193-208, 1993). The dilution that gives 50% cytopathic effect was determined by the interpolating procedure of Reed and Muench, as described by E. Rodriguez-Boulan (Methods Enzymol. 98: 486-501, 1983). Results from a representative experiment are shown. Each experiment was repeated at least 3 times.

Results and conclusions: The results shown in Fig. 6a) indicates that CTC8 is a potent inhibitor of HSV-1 virus replication, with an ID50 = 0.2 μM (ID50 = 50% inhibitory dose). The antiviral activity occurs at concentrations non-toxic to the cells, as the LD50 (lethal dose 50%) was determined to be 35 μM by MTT assay in the same cell line, with a selective index (S.I.) = 175. CTC7 has a weaker antiviral activity than CTC8, with an ID50 = 3 μM. CTC8 is shown to be at least 100 times more active in reducing HSV-1 yield than cyclopent-2-en-1-one (ID50= 60 μM; S.I. = 12.5) and reduces HSV-1 yield by 99.997% at concentrations below the LD_{50}.

Figure 6b) provides a comparison of the antiviral activity of CTC8 with that of Aciclovir over a range of concentrations.

Table 1 below provides IC values based upon Figures 6a) to c).

Table 1

HSV-1	IC50	IC90	IC99	IC99.9
Aciclovir	(0.02 μM)	0.1 μM	0.8 μM	100μM
CTC-8	0.2 μM	0.3 μM	1.4 μM	5μM

(The brackets indicate that the figure is an extrapolated one.)

Example 3: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the replication of Sendai virus.

Methods: Monkey kidney 37RC cells were grown at 37°C under the conditions described in Example 1 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/10^5 cells) for 1 h at 37°C, and then treated with different concentrations of CTC8, CTC7 or CTC1. Virus yield at 24 hours after infection was determined in the supernatant of infected cells by HAU titration. Results from a representative experiment are shown. Each experiment was repeated at least 3 times.

Results and conclusions: The results shown in Fig. 7 indicate that CTC8 is a potent inhibitor of Sendai virus replication, with an ID50 = to 0.1 μM. CTC7 has a weaker antiviral activity than CTC8, with an ID50 = 2 μM. CTC8 is shown to be at least 100 times more active in reducing Sendai virus yield than cyclopent-2-en-1-one (ID50= 90 μM).

Table 2 below provides IC values based upon Figure 7.

Table 2

Sendai	IC50	IC90	IC99
CTC-8	0.1 μM	1.6 μM	8.3 μM

Example 4: Evidence for anti-inflammatory effects of CTC-8

Immune cells such as neutrophils and macrophages are activated in response to injury and infection. When activated they produce nitric oxide and superoxide radicals to kill foreign cells and cancer cells. They also produce a variety of cytokines and chemokines to cause further recruitment of immune cells in a cascade leading to the cardinal symptoms of inflammation; heat, redness, swelling, pain, and loss of function.

A key signalling step in the activation of the immune cells is the transcription factor *nuclear factor κB* (NF-κB) (16). NF-κB regulates the transcription of a spectrum of pro-inflammatory genes such as IL-1, IL-2, TNF-α, ICAM-1, VCAM-1, and E-selectin as well as the inducible form of nitric oxide synthase (iNOS) and cyclo-oxygenase II.

Thus the activation of NF-κB occupies a critical position in the inflammatory cascade. As cyclopentenone prostaglandins are known to have anti-inflammatory actions (17), the cyclopentenone derivative CTC-8 was tested for its effects on the induction of iNOS in a mouse macrophage model.

Mouse macrophages of the cell line RAW264.7 were stimulated with gamma interferon and 0.1 U/ml of bacterial lipopolysaccharide (LPS) in 96-well plates (17). The induction of iNOS was measured by determination of the levels of nitrite (NO_2^-) formed in the supernatant, using the Griess reagent. The natural cyclopentenone prostaglandin PG-J_2 was used for comparison.

CTC-8 had a concentration-dependent inhibitory effect on nitrite formation at submicromolar concentrations (Fig. 8). At a concentration of 3μg/ml the level of nitrites was reduced to background levels. PG-J_2 had similar effects but was much less potent. No evidence of cytotoxicity was seen for either CTC-8 or PG-J_2. The

results of this experiment indicated that the induction of the pro-inflammatory iNOS gene by interferon gamma and LPS treatment is suppressed by CTC-8. The most likely explanation is that CTC-8 is inhibiting the activation of the NF-κB pathway.

Table 3 below shows IC50 values obtained for PGJ_2 and CTC-8 in respect of the inhibition of nitrite formation.

Table 3	
INOS	IC50
PG-J2	(11.0 μg/ml)
CTC-8	0.79 μg/ml

(The brackets indicate that the figure is an extrapolated one.)

Example 5: Evidence that CTC-8 does not lower blood pressure:

Most prostaglandins have strong effects on vascular smooth muscle, and will lower blood pressure in animals and humans. The cyclopentenone derivative CTC-8 was therefore tested for its effect on the blood pressure of the anaesthetized rat. Prostaglandins A_1 and E_1 were used for comparison.

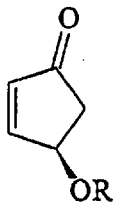
Male Wistar rats were anaesthetized and test drugs were infused intravenously. Blood pressure and heart rate were recorded from the femoral artery

Prostaglandins A_1 and E_1 caused dose-dependent falls in blood pressure in doses from 30μg/kg/min (Fig. 9). CTC-8 at doses from 60-1200μg/kg/min had no effect on blood pressure. At the higher dose a small fall in blood pressure was observed but this was not different from that of solvent alone.

These results indicate that CTC-8 may be devoid of the generalised effects on smooth muscle characteristic of natural cyclopentenone prostaglandins.

Example 6: Preparation of compounds suitable for use in the present invention

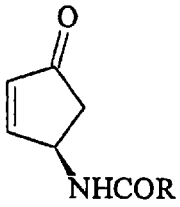
Compounds of type (1) are prepared according to literature methods. (18)



for example
R = $SiMe_2{}^tBu$

(1)

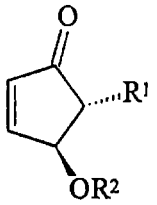
Compounds of type (2) are prepared as illustrated in Scheme 1.(19)



for example
R = Ph

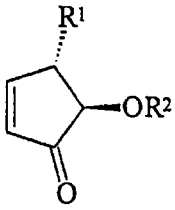
(2)

Compounds of type (3) are readily prepared from furfural (Scheme 2). (20)



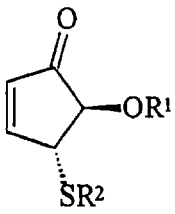
(3)

Compounds of type (4) are prepared from norbornadiene (Scheme 3). (21)

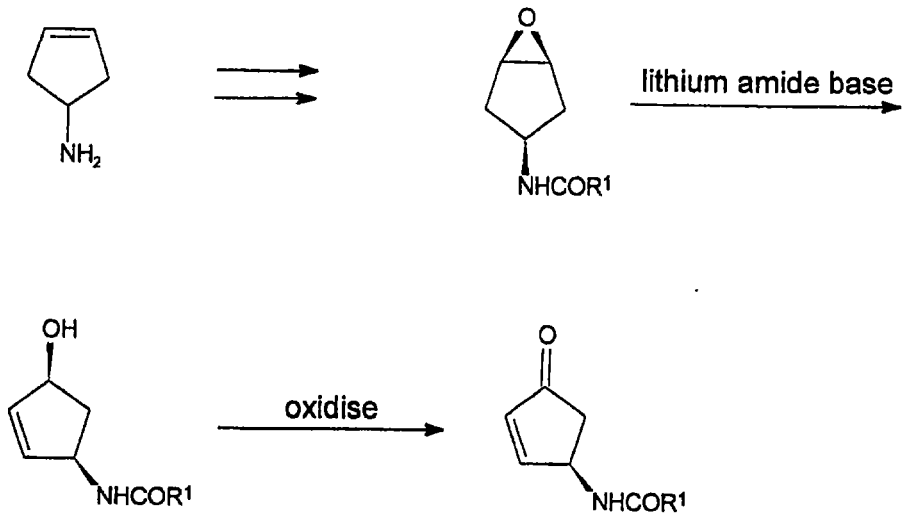


(4)

Finally compounds of type (5) are prepared as shown in Scheme 4. (22)

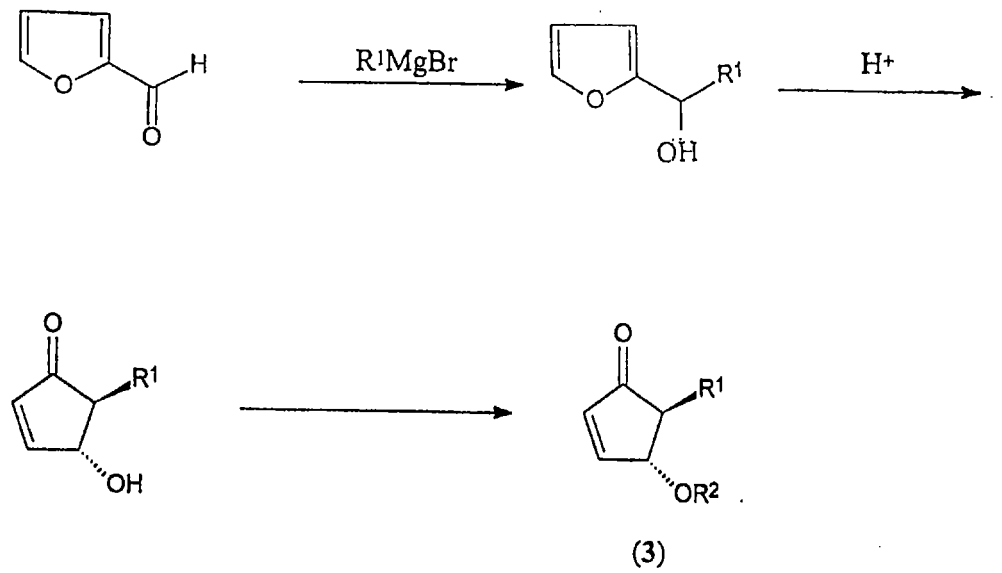


(5)



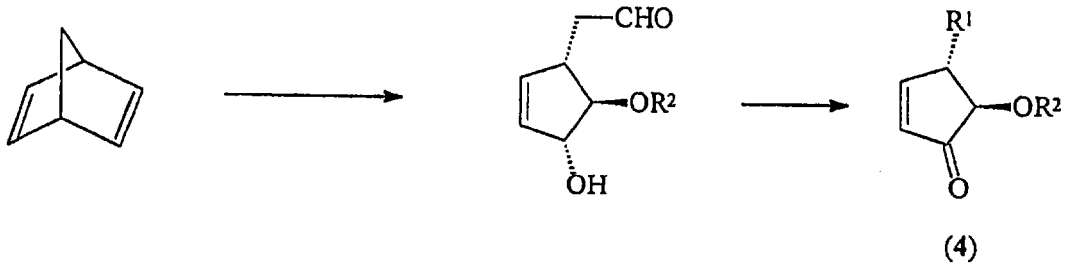
(2)

Scheme 1



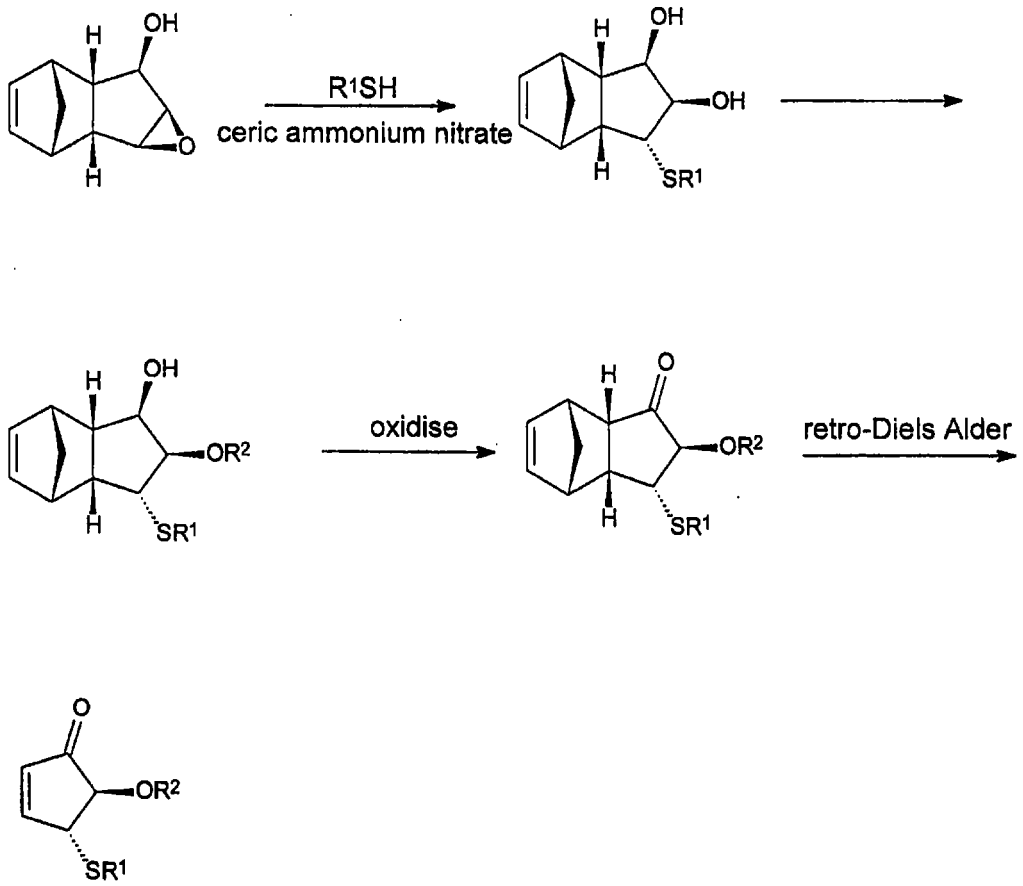
(3)

Scheme 2



(4)

Scheme 3


H
OH
O
H
R1SH
ceric ammonium nitrate
H
OH
OH
H
SR1
H
OH
OR2
H
SR1
oxidise
H
O
OR2
H
SR1
retro-Diels Alder
O
OR2
SR1

(5)

Scheme 4

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 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.

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.* Birkhaüser Verlag, Basel Boston Berlin, 1996.
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, Birkhaüser Verlag, Basel Boston Berlin) pp. 337-357, 1996.
6. Santoro MG, Garaci 9, 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, 1032-1034, 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.
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 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. H. Zeng, L. He and Z. Liu, *Tetrahedron Asymm.*, 1993, 4, 2277-2278

19. M. Asami, M. Ogawa and S. Inoue, *Tetrahedron Lett.*, 1999, 40, 1563-1564

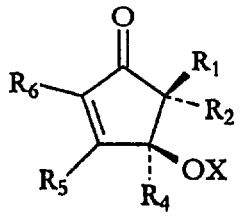
20. G. Piancatelli, A Scettri and S. Barbado, *Tetrahedron Lett.*, 1976, 39, 3555-3558, G. Piancatelli, M. D'Auria and F. D'Onofrio, Synthesis, 1994, 867-889, F. West and G. Gunawardena, *J.Org. Chem.*, 1993, 58, 5043-5044

21. A. Baxter et al., *J. Chem. Soc., Perkin Trans. 1*, 1986, 889

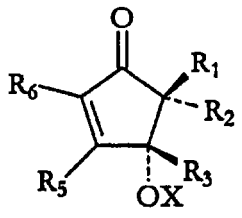
22. N. Iranpoor, N. Baltrok and F. Zardaloo, *Tetrahedron*, 1991, **47**, 9861-9866

Claims

1. A compound for use in medicine with formula (a) or (b):-



(a)



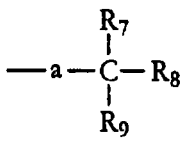
(b)

wherein: R_1 and R_2 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic,

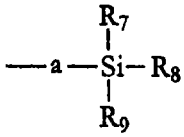
R_3 and R_4 are hydrogen,

R_5 and R_6 are, independently, hydrogen or a halogen,

and X has the formula:-

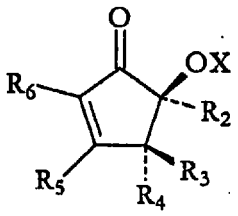


or

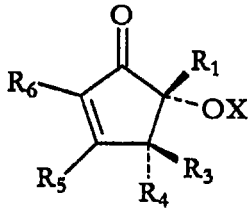


wherein R_7, R_8 and R_9 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic, and "a" is absent or a linking group, optionally a hydrocarbyl linking group;

or with formula (c) or (d):-



(c)



(d)

wherein: R_1 and R_2 are hydrogen,

R_3 and R_4 are, independently, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or heteroalicyclic, and

R_5, R_6 and X are as defined above.

2. A compound as claimed in claim 1 having formula (a) or (b).

3. A compound as claimed in claim 1 or claim 2 having higher activity than cyclopent-2-en-1-one 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.

4. A compound for use in medicine according to any preceding claim, wherein X is an Si-containing group.

5. A compound for use in medicine according to any preceding claim, wherein R_7, R_8 and R_9 are substituted alkyl, aryl or substituted aryl.

6. A compound for use in medicine according to any preceding claim, wherein X comprises at least 4 carbon atoms.

7. A compound for use in medicine according to claim 1 or any of claims 3-6, said compound having formula (c) or (d), wherein R_3 and/or R_4 comprises no more than 7 carbon atoms.

8. A compound for use in medicine according to claim 1 or any of claims 3-6, said compound having formula (c) or (d), wherein a hydrocarbyl side chain is not present at positions R_3 and/or R_4.

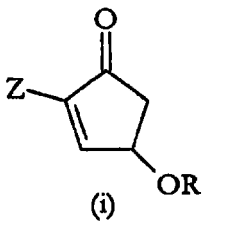
9. A compound for use in medicine according to claim 8, wherein R_3 and/or R_4 is hydrogen.

10. R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one for use in medicine.

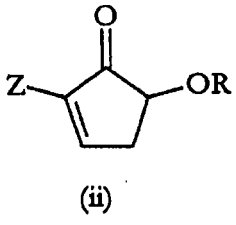
11. S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one for use in medicine.

12. A compound for use in medicine according to any of claims 1 – 9 which is an S-enantiomer.

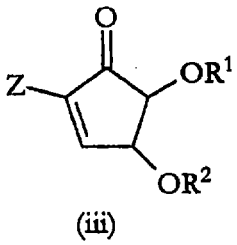
13. A compound for use in medicine with formula (i), (ii), (iii) or (iv):-



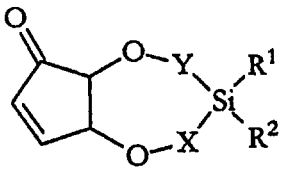
(i)



(ii)



(iii)



(iv)

wherein Z is hydrogen or a halogen, R is an optionally substituted hydrocarbyl group including up to 8 carbon atoms, or a moiety incorporating at least one heteroatom and up to 50 carbon atoms, at least one of R^1 and R^2 in formula (iii) incorporates one or more heteroatoms and up to 30 or 50 carbon atoms, at least one of R^1 and R^2 in formula (iv) is an optionally substituted hydrocarbyl group, and X and Y are absent or are linking groups.

14. The use of a compound in the preparation of a medicament for treating a viral-mediated disorder, wherein the compound is as described in any of claims 1 to 13.

15. The use of a compound in the preparation of a medicament for treating a bacterial-mediated disorder, wherein the compound is as described in any of claims 1 to 13.

16. The use of a compound in the preparation of a medicament for treating a disorder mediated by radiation, wherein the compound is as described in any of claims 1 to 13.

17. The use of a compound in the preparation of a medicament for treating an inflammatory disorder, wherein the compound is as described in any of claims 1 to 13.

18. The use of a compound in the preparation of a medicament for treating a disorder of the immune system, wherein the compound is as described in any of claims 1 to 13.

19. The use of a compound in the preparation of a medicament for treating ischemia, wherein the compound is as described in any of claims 1 to 13.

20. The use of a compound in the preparation of a medicament for treating arteriosclerosis, wherein the compound is as described in any of claims 1 to 13.

21. The use of a compound in the preparation of a medicament for treating a disorder involving cell proliferation, wherein the compound is as described in any of claims 1 to 13.

22. The use according to claim 21, wherein the disorder is a cancer.

23. The use of a compound in the preparation of a medicament for treating a disorder involving damage to cells or killing of cells, wherein the compound is as described in any of claims 1 to 13.

24. The use of a compound in the preparation of a medicament for treating diabetes, wherein the compound is as described in any of claims 1 to 13.

25. The use of a compound in the preparation of a medicament for treating a disorder involving calcium loss or deficiency, wherein the compound is as described in any of claims 1 to 13.

26. The use of a compound in the preparation of a medicament for treating a viral disorder affecting aquatic organisms, wherein the compound is as described in any of claims 1 to 13.

27. The use of a compound in treating a viral disorder affecting plants, wherein the compound is a compound as described in any of claims 1 to 13.

28. The use of a compound as a research tool for the analysis of one or more of the following: HSF, NF-κB, 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, disorders involving damage to, or killing of cells, or diabetes; disorders involving calcium loss or deficiency, disorders affecting aquatic organisms or plant disorders, wherein the compound is as described in any of claims 1 to 13.

29. A novel compound having a formula as described in claim 13, wherein the compound is not R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one or S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one.

30. A pharmaceutical composition comprising a compound as described in any preceding claim and optionally including a pharmaceutically acceptable carrier.