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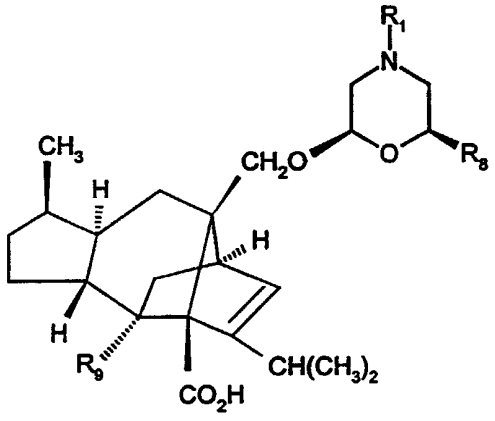

(I)

(57) Abstract: Compounds of formula (I) and physiologically acceptable salts and or metabolically labile derivatives thereof, wherein R_1 represents a group selected from CXR_2, $CXOR_3$, $CONHR_4$ or SO_2R_5; X is oxygen or sulphur; R_8 represents a group selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-6} straight or branched chain alkenyl, optionally substituted phenyl or C_{1-4} alkyl substituted with a group selected from C_{1-4}alkoxy, hydroxy, acyloxy, alkoxy carbonyl or aryloxycarbonyl, and R_9 represents a group selected from formyl or cyano, processes for their preparation, pharmaceutical compositions containing then and their use in medicine.

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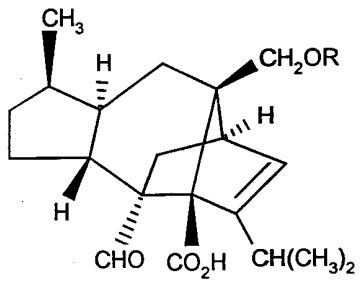
CARBOCYCLIC DERIVATIVES

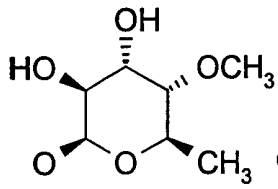
This invention relates to novel carbocyclic derivatives having antifungal activity. More particularly it relates to novel sordaricin derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, more particularly in the prevention or treatment of diseases in animals, including humans, caused by fungal infection.

British Patent Specification No. 1,162,027 describes the preparation of an antibiotic, SL2266, by the cultivation of the strain NRRL 3196 of the fungus species Sordaria araneosa. SL 2266, later named sordarin, is reported to have fungistatic activity. The same research group also described in Helvetica Chimica Acta (1971), 51, 119-120 the degradation of sordarin to sordaricin. Published Japanese Patent Application No. J6 2040292A describes the preparation of an antibiotic, zofimarin, which is reported to have antifungal activity.

Sordarin, sordaricin and zofimarin may be represented by formula (A) below

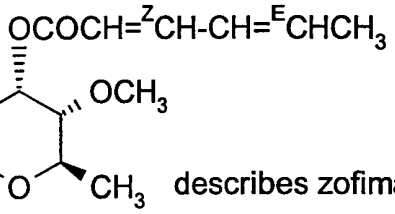


(A)



where OR as O describes sordarin;

OR as OH describes sordaricin; and

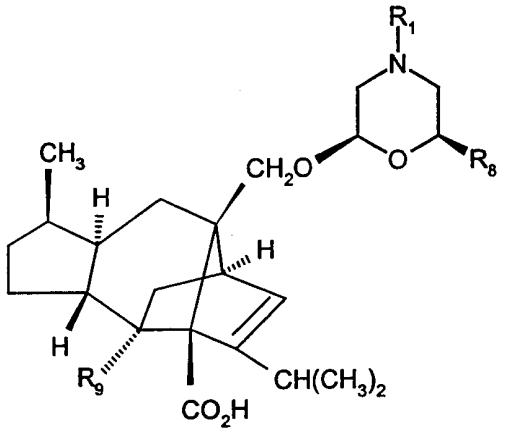
OR as  describes zofimarin.

Although sordarin and zofimarin exhibit antifungal activity, both compounds are only moderately active and have limited spectra of action when tested against a battery of fungal organisms.

WO96/14326 and WO96/14327 describe novel sordarin derivatives which exhibit useful antifungal activity. WO99/09974 and WO99/09975 describe 4-cyano-4-deformyl sordarin and sordaricin derivatives which exhibit antifungal activity.

We have now found a novel group of sordaricin derivatives which exhibit a useful spectrum of antifungal activity and which can be conveniently prepared from readily available starting material.

Thus according to a first aspect of the invention, we provide compounds of formula (I).



(I)

and physiologically acceptable salts and or metabolically labile derivatives thereof, wherein R_1 represents a group selected from CXR_2, $CXOR_3$, $CONHR_4$ or SO_2R_5;

X is oxygen or sulphur;

R_2 is a group selected from C_{1-6} straight or branched chain alkyl, C_{2-6} straight or branched chain alkenyl, C_{2-6} straight or branched chain alkynyl, C_{1-4} straight or branched chain alkyl substituted by a group selected from (C_{1-4}alkoxy, hydroxy, halogen, C_{1-4}alkoxycarbonyl, carboxy or optionally substituted phenyl), optionally substituted phenyl, or optionally substituted 5 or 6 membered heteroaryl group or optionally substituted C_{5-7} cycloalkyl or C_{1-6} alkoxycarbonyl, R_3 is a group selected from C_{1-6} straight or branched alkyl, C_{2-6} straight or branched alkenyl or alkynyl or C_{1-4} straight or branched alkyl substituted by a group selected from C_{1-4}alkoxy, hydroxy, halogen, carboxy, C_{1-4} alkoxycarbonyl or optionally substituted phenyl; R_4 represents C_{1-6} straight or branched alkyl, or optionally substituted phenyl; R_5 represents C_{1-6} straight or branched alkyl, optionally substituted phenyl or the group NR_6R_7 wherein R_6 and R_7 independently represent hydrogen or C_{1-4} straight or branched alkyl;

R_8 represents a group selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-6} straight or branched chain alkenyl, optionally substituted phenyl or C_{1-4} alkyl substituted with a group selected from C_{1-4}alkoxy, hydroxy, acyloxy, alkoxy carbonyl or aryloxycarbonyl, and R_9 represents a group selected from formyl or cyano.

Physiologically acceptable salts of the compounds of formula (I) include salts formed with physiologically acceptable bases as well as internal salts.

Suitable physiologically acceptable salts of the compounds of formula (I) with bases include inorganic base salts such as alkali metal salts (for example sodium and potassium salts) and ammonium salts and organic base salts. Suitable organic base salts include amine salts such as trialkylamine (e.g. triethylamine), dialkylamine (e.g. dicyclohexylamine), optionally substituted benzylamine (e.g. phenylbenzylamine or p-bromobenzylamine), procaine, ethanolamine, diethanolamine, N-methylglucosamine and tri(hydroxymethyl)methylamine salts and amino acid salts (e.g. lysine and arginine salts).

References hereinafter to a compound of formula (I) includes that compound and physiologically acceptable salts thereof.

Other salts which are not physiologically acceptable may be useful in the preparation of compounds of formula (I) and these form a further aspect of the invention.

Metabolically labile derivatives of compounds of formula (I) are compounds which are converted in the body into compounds of formula (I). Examples of such derivatives include conventional metabolically labile esters formed from the free carboxylic acid in the molecule. It is well known in the field of medicinal chemistry that there is a wide range of structurally distinct esters of carboxylic acid which are readily hydrolysed in the body to yield the parent carboxylic acid or a salt thereof and it is to be understood that the present invention encompasses all such esters.

Examples of suitable esters include phthalidyl, (2-oxo-5-methyl-1,3-dioxolen-4-yl) methyl or those derived from the alcohol HOCH(R_a) OCO(0) pR_b, wherein R_a is hydrogen or C_{1-4}alkyl, p is zero or 1 and R_b is a group selected from C_{1-6}alkyl (optionally substituted by one or two groups selected from amino, C_{1-4}alkylamino, di(C_{1-4}alkyl) amino or carboxyl), C_{5-8}cycloalkyl (optionally substituted by C_{1-3}alkyl or carboxyl), C_{1-4}alkyl subsituted by C_{1-3} alkoxy, phenyl (optionally subsituted, by carboxyl, aminoalkyl, C_{1-4}alkylaminoalkyl or di (C_{1-4}alkyl) amino alkyl e.g. dimethylaminomethyl) or R_b is a 5 to 8 membered

heterocyclic ring containing one or 2 hetero groups selected from oxygen or NH e.g. piperedino-4-yl or tetrahydropyran-2-yl.

It is to be understood that the present invention encompasses any individual isomers including rotamers and optical isomers, of compounds represented by formula (I) above as well as mixtures thereof, including wholly or partially racemic mixtures thereof.

The term straight or branched chain alkyl (C_{1-4} or C_{1-6} alkyl) includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl, pentyl, isopentyl, 1-ethylpropyl, hexyl or isohexyl.

The term C_{1-4}alkoxy as a group or part of a group refers to straight or branched alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy.

The term C_{2-6} alkenyl as a group or part of a group include such groups as ethenyl, 1-methylethenyl, 2-methylethenyl, or allyl.

The term optionally substituted phenyl as a group or part of a group e.g. phenylalkyl includes phenyl or phenyl substituted by 1, 2 or 3 groups which may be the same or different and selected from C_{1-4}alkyl, halogen (fluorine, chlorine, bromine or iodine), hydroxy, C_{1-4}alkoxy, methylenedioxy, trifluoromethyl or acetylamino.

The term optionally substituted C_{5-7} cycloalkyl includes cyclopentyl, cyclohexyl or cycloheptyl group which may be substituted by 1 or 2 methyl, methoxy, hydroxy or phenyl groups.

The term straight or branched C_{2-6}alkynyl includes ethynyl, 2-methyl-ethynyl or propynyl.

The term 5 or 6 membered heteroaryl group refers to a heteroaryl group wherein the 5 membered group contains a single heteroatom selected from oxygen, sulphur or nitrogen and optionally contains 1 or 2 further nitrogen atoms, and the

6 membered group contains from 1 to 3 nitrogen atoms. Examples of such heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, iso-oxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidiyl, pyridazinyl, pyrazinyl or triazinyl. The said heteroaryl groups may be substituted by one or two groups selected from C1-4alkyl e.g. methyl, hydroxyalkyl e.g. heteroaryl, acyloxyalkyl e.g. acetoxymethyl, halogen, or phenyl or the heteroaryl ring may be fused to a phenyl ring e.g. a benzothienyl or benzofuranyl.

When R_1 is the group CXR_2 examples of suitable R_2 groups include C_{1-6}alkyl (e.g. methyl, ethyl, isopropyl, butyl or 2,2-dimethylpropyl), C_{1-4} alkyl substituted by methoxy (e.g. methoxymethyl), C_{1-4} alkyl substituted by optionally substituted phenyl (e.g. benzyl), C_{1-4} alkyl substituted by C_{1-4} alkoxycarbonyl (e.g. ethoxycarbonylmethyl), C_{2-6} alkenyl (e.g. ethenyl or 1-methylethenyl), optionally substituted phenyl (e.g. phenyl optionally substituted by halogen (such as fluorine), or methoxy, C_{5-7}cycloalkyl (e.g. cyclohexyl), heteroaryl, e.g. furanyl, thienyl, oxazolyl, triazolyl, e.g. 2-phenyl-4-methyl, 1,2,3-triazol-5yl, benzofuranyl, benzothienyl, or pyridyl, or R_2 is C_{1-4} alkoxycarbonyl group e.g. ethyloxycarbonyl group.

When R_1 is the group $CXOR_3$ examples of suitable R_3 groups include alkyl e.g. methyl, ethyl or C_{2-6} alkenyl e.g. ethenyl or 1-methylethenyl.

For the groups CXR_2 and $CXOR_3$ X is conveniently oxygen.

When R_1 is the group $CONHR_4$, examples of suitable R_4 group include alkyl e.g. ethyl or optionally substituted phenyl e.g. phenyl.

When R_1 is the group SO_2R_5 examples of suitable R_5 groups include alkyl e.g. methyl, optionally substituted phenyl e.g. phenyl or phenyl substituted by acetylamino, or R_5 is a dialkylamino group e.g. dimethylamino.

Conveniently R_1 is a group selected from CXR_2 or $CXOR_3$.

When R_8 is C_{1-6} alkyl examples of suitable groups include methyl, ethyl, propyl, butyl or t-butyl.
When R_8 is optionally substituted phenyl an example of a suitable groups includes phenyl.

Conveniently R_2 is a group selected from C_{1-6}alkyl such as methyl, ethyl, isopropyl, butyl or 2,2 dimethylpropyl, C_{2-4}alkenyl such as ethenyl, C_{1-4}alkyl substituted by methoxy e.g. methoxymethyl. C_{1-4}alkyl substituted by halogen (such as chlorine e.g. chloromethyl), C_{1-4}alkyl substituted by alkoxycarbonyl (e.g. alkoxycarbonylmethyl such as ethoxycarbonylmethyl), C_{1-4}alkyl substituted by optionally substituted phenyl (e.g. benzyl), C_{1-4}alkoxycarbonyl e.g. ethoxycarbonyl, optionally substituted phenyl such as phenyl, fluorophenyl, methoxyphenyl or trimethoxyphenyl, C_{5-7}-cycloalkyl such as cyclohexyl or heteroaryl such as furanyl, thienyl, isoxazole, pyridyl, a 1,2,3 triazole such as 4-methyl-2-phenyl-1,2,3-triazolyl, or benzothienyl.

Conveniently R_3 is a group selected from C_{1-4} alkyl e.g. methyl or C_{2-4} alkenyl e.g. 1-methylethenyl.

The group R_4 is conveniently C_{1-4} alkyl e.g. ethyl or optionally substituted phenyl e.g. phenyl.

The group R_5 is conveniently C_{1-4} alkyl e.g. methyl optionally substituted phenyl e.g. phenyl or 4-acetylaminophenyl or NR_6R_7 such as dimethylamino.

The group R_8 is conveniently C_{1-6} alkyl such as methyl, ethyl, propyl, butyl or t-butyl or phenyl.

A preferred class of compounds of formula (I) are those wherein R_1 is the group CXR_2 or $CXOR_3$ and X is oxygen.

A further preferred class of compounds of formula (I) are those wherein R_9 is a formyl group.

Yet a further preferred class of compounds are those wherein R_8 is a methyl group.

A preferred group of compounds of formula (I) are those wherein R_8 is methyl and R_9 is formyl. Within this group particularly preferred compounds are those wherein R_1 is CXR_2 or $CXOR_3$ and X is oxygen.

The compounds of formula (I) are useful in combating fungal and or protozoal infections in animals, including humans. For example, they may be used in the treatment of fungal infections including those caused by one or more organisms such as species of Candida (e.g. Candida albicans, Candida glabrata, (Torulopsis glabrata), Candida tropicalis, Candida parapsilosis and Candida pseudotropicalis), Cryptococcus neoformans, Aspergillus Spp (e.g. Aspergillus flavus and Aspergillus fumigatus), Coccidioides (e.g. Coccidioides immitis), Paracoccidioides (e.g. Paracoccidioides brasiliensis), Histoplasma (e.g. Histoplasma capsulatum) or Blastomyces (e.g. Blastomyces dermatitidis). They may also be used to treat other fungal infections caused by species of Trichophyton, Microsporum or Epidermophyton (e.g. Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum canis or Epidermophyton floccosum), or in mucosal infections caused by Candida albicans.

Compounds of formula (I) may also be used to treat other infections caused by other fungi such as Geotrichum (e.g. Geotrichum clavatum), Trichosporon (e.g. Trichosporon beigelii), Blastoschizomyces (e.g. Blastoschizomyces capitatus), Sporothrix (e.g. Sporothrix schenckii), Scedosporium (e.g. Scedosporium apiosperum), Cladosporium (e.g. Cladosporium carrionii) and Pityrosporum ovale.

The compounds of formula (I) may also be used to treat infections caused by protozoa such as Toxoplasma, Cryptosporidium, Leishmania, Tripanosoma, Giardia and Trichomonas.

The compounds of formula (I) may also be used to treat infections caused by Pneumocystis Carinii.

The antifungal activity of the compounds of formula (I) may be determined using conventional in vitro and in vivo screens. Thus, the in vitro evaluation of the anti-fungal activity of compounds of the invention was performed on liquid or solid medium by the anti-fungal two-fold serial dilution technique of determining the minimum inhibitory concentration (MIC) of anti-fungal agent that inhibited development of growth after 24 to 48 hours of incubation at 37°C. In practice, a series of agar plates or broth microdilution panels containing two-fold dilutions of anti-fungal agent tested were inoculated with a standard culture of a clinically relevant pathogen, for example, Candida albicans. The agar plates or broth microdulution panels were then examined for the presence or absence of growth of the fungus and the appropriate MIC values were noted.

MFC values (defined as the lowest anti-fungal concentration that killed at least 99.9% of the initial inoculum in liquid medium) may also be determined by sub-culturing 0.01 and 0.1μl of broth from the drug-free control well, the first well containing growth and each clear well on agar plates.

The fungicidal activity of the compounds of formula (I) may also be determined in conventional tests in animals e.g. rats and mice. For example the lethal systems candidiasis test in mice.

The compounds of formula (I) may also be useful in the control and or eradication of phytopathogenic fungi.

Compounds of the invention show particularly useful activity against one or more of the organisms selected from Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, Pneumocystis carinii Coccidioides immitis, Paracoccidioides brasiliensis, Histoplasma capsulatum and Blastomyces dermatitides.

In view of their antifungal and or antiprotozoal activity, compounds of formula (I) recommend themselves for the treatment of a variety of fungal and or protozoal infections in human beings and animals. Such infections include superficial, cutaneous, subcutaneous and systemic mycotic infections such as respiratory tract infections, gastrointestinal tract infections, cardiovascular infections, urinary

tract infections, CNS infections, candidiasis and chronic mucocandidiasis (e.g. thrush and vaginal candidiasis) and skin infections caused by fungi, cutaneous and mucocutaneous candidiasis, dermatophytoses including ringworm and tinea infections, athletes foot, paronychia, pityriasis versicolor, erythrasma, intertrigo, fungal nappy rash, candida vulvitis, candida balanitis and otitis externa. They may also be used as prophylactic agents to prevent systemic and topical fungal infections. Use as prophylactic agents may, for example, be appropriate as part of a selective gut decontamination regimen in the prevention of infection in immunocompromised patients (e.g. AIDS patients, patients receiving cancer therapy or transplant patients). Prevention of fungal overgrowth during antibiotic treatment may also be desirable in some disease syndromes or iatrogenic states. They may also be used in the prophylaxis and or treatment of infections caused by Pneumocystis carinii.

Thus in a further aspect the invention provides a method of the treatment of human or non human animal body to prevent or treat fungal and or protozoal diseases, which method comprises administering to solid body an effective amount of a compound of formula (I).

The invention also provides for the use of a compound of formula (I) in the manufacture of a medicament for the treatment or prevention of fungal and or protozoal infections.

While it is possible that, for use in therapy, compounds of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising compounds of formula (I) and physiologically acceptable salts thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, implant, rectal, topical, ophthalmic or genito-urinary administration or in a form suitable for administration by inhalation or insufflation.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate or crosscarmellose sodium; wetting agents such as sodium lauryl sulphate and pH modifiers for example citric acid, malic acid, tartaric acid, sodium carbonate, sodium bicarbonate, triethanolamine or trometamol. The capsule may contain powders, tablets, pellets, granules, liquids, waxes, surfactants or any combination of the former, which may be coated according to the methods well known to the art. The content of the capsules can be made of: binding agents, fillers, lubricants, desintegrants, wetting agents and pH modifiers, as described above. The tablets which include chewable, dispersible or effervescent tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid and flavouring agent.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation the compositions according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch or as a modified physical form of the drug substance alone. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The compositions may take the form of a suppository, e.g. containing a conventional suppository base, or a pessary, e.g. containing a conventional pessary base.

The compositions may also be formulated for topical administration in the form of ointments, creams, gels, lotions, shampoos, powders (including spray powders), pessaries, tampons, sprays, dips, aerosols, drops (e.g. eye, ear or nose drops) or pour-ons. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening

and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components. Pour-ons may, for example, be formulated for veterinary use in oils containing organic solvents, optionally with formulatory agents, e.g. stabilising and solubilising agents. Pessaries and tampons for vaginal insertion may be formulated using conventional techniques and, where appropriate, may contain an effervescent vehicle. Such compositions may also contain other active ingredients such as corticosteroids, antibiotics or antiparasitics as appropriate.

Liquid preparations for intranasal delivery may take the form of solutions or suspensions and may contain conventional excipients such as tonicity adjusting agents, for example, sodium chloride, dextrose or mannitol; preservatives, for example benzalkonium chloride, thiomersal, phenylethyl alcohol; and other formulating agents such as suspending, buffering, stabilising, dispersing and or flavouring agents.

Transdermal administration may be affected by the design of a suitable system which promotes absorption of the active compound through the skin and would typically consist of a base formulation enclosed within an adhesive stick-on patch comprising backing films, membranes and release liners. Such systems may include absorption enhancers such as alcohols or work by promoting ionotophoresis.

The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, a compound of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

When the compositions comprise dosage units, each unit will preferably contain 0.001mg to 1000mg, advantageously 0.01mg to 400mg, of active ingredient where a compound of the invention is to be administered orally. The daily dosage as employed for adult human treatment will preferably range from

0.001mg to 5000mg of active ingredient, most preferably from 0.01mg to 2000mg which may be administered in 1 to 4 daily doses, for example, depending on the route of administration and on the condition of the patient and the disease to be treated.

The compound may be administered by intravenous infusion using, for example, up to 50mg/kg/day of the active ingredient. The duration of treatment will be dictated by the rate of response rather than by arbitrary numbers of days.

Compounds of the invention may also be used in combination with other therapeutic agents, and the invention thus provides, in a further aspect, a combination comprising a compound of the invention together with another therapeutically active agent.

Thus for example the compounds of the invention may be used in combination with one or more other antifungal agents, such as a polyenic derivative e.g. (Amphotericin B, Nystatin, a lipid formulation of Amphotericin B) an azole derivative e.g. (Fluconazole, Intraconazole, Ketoconazole, Miconazole, Clotrimazole, ZD-08070, UK-109496), 5-Fluorocytosine, a Pneumocandin or Echinocandin derivative (such as Cilofungin, LY-303366, L-733560), an allylamine derivative (e.g. Terbinafine, Butenafine or Naftifine), and/or one or more immunomodulating agents such as an interferon e.g. (IFN-γ), interleukine e.g. (IL-1, IL-2, IL-3 and IL-8) and colony stimulating factors, [(G)-CSF, (M)-CSF and (GM)-CSF] and defensines. Particularly advantageous compounds for use with compounds of the invention include Intraconazole, Flucytosine, Fluconazole, Terbinafine or Amphotericin B.

When the compounds of the invention are administered in combination with another antifungal agent the compounds of the invention and the other fungal agent can be administered at the recommended maximum clinical dosage or at lower doses.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically

acceptable carrier thereof comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of the invention is used in combination with a second therapeutic agent against the same condition the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

According to another aspect of the present invention, we provide a compound of formula (I) or a physiologically acceptable salt thereof or a pharmaceutical composition comprising a compound of formula (I) or a physiologically acceptable salt thereof as defined above for use in therapy, particularly for the treatment of fungal infections in animals (especially humans).

According to another aspect of the present invention, we provide the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of fungal infections in a human or non-human animal patient.

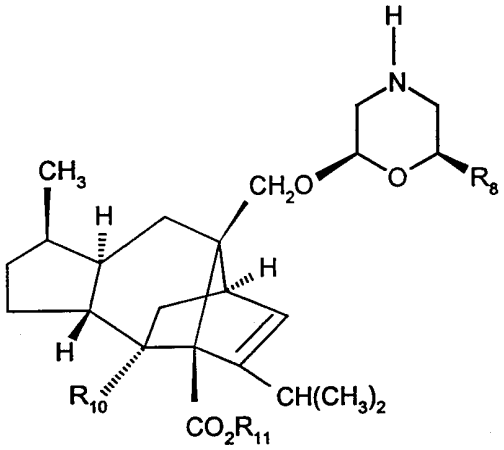
According to a further aspect of the present invention, we provide a method of treatment of the human or non-human animal body to combat fungal diseases, which method comprises administering to said body an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

It will be appreciated by those skilled in the art that references herein to treatment extend to prophylaxis as well as the treatment of established conditions or infections.

For use as against phytopathogenic fungi the compounds may be formulated in conventional manner.

The invention also provides processes for the preparation of compounds of formula (I).

Thus the invention provides a process for the preparation of compounds of formula (I) or a physiologically acceptable salt thereof which comprises reacting a compound of formula (II) wherein R_8 has the meaning given in formula 1, R_{10} is cyano formyl, or a protected formyl group and R_{11} is hydrogen, a carboxyl protecting or a cation of a salt,



(II)

with a compound capable of introducing the group R_1 followed where necessary or desired by removal of one or more protecting groups and isolation of the compound in the form of the free acid or a salt thereof.

When R_{10} is a protected formyl group this is conveniently an acetal thereof such as those formed with a C_{1-4} alkanol e.g. methanol or ethanol or a 1,2 or 1,3 diol such as ethylene glycol, 1,2-propanediol or 1,3-propanediol.

When R_{11} is a carboxyl protecting group this is conveniently a substituted methyl group such as optionally substituted benzyl, diphenylmethyl, allyl or trialklsilylalkyloxy-methyl e.g. trimethylsilylethyloxymethyl.

Suitable reagents capable of introducing the group R_1 include activated derivatives of the acids R_2CXOH, R_3OCXOH, $R_4NHCO2H$, or R_5SO2OH or the isocyanate R_4NCO, wherein the groups R_2, R_3, R_4 and R_5 have the meaning given in formula 1.

Conveniently the activated derivative of the above acids are the corresponding acid halides e.g. chlorides such as R_2CXCl, R_3OCXCl, $R_4NHCOCl$ or R_5SO_2Cl.

When R_1 is the group R_2CO alternative suitable activated derivatives of the acid R_2CO_2H include those derived from the couping agents commonly used in peptide synthesis, for example activated derivatives formed with carbodimides or carbonyldiimidazole or a mixed acid anhydride.

The reaction with the activated acid derivatives is preferably carried out in an aprotic solvent e.g. a hydrocarbon, halohydrocarbon e.g. dichloromethane, or an ether and in the presence of a base such as an alkali metal carbonate, or bicarbonate or a tertiary organic amine, e.g. a trialkylamine or an optionally substituted pyridine.

The carboxyl protecting group R_{11} may be removed by conventional means. Thus when R_{11} is an arylmethyl group it may be removed by hydrogenolysis using hydrogen and a suitable catalyst e.g. Palladium on charcoal in a suitable solvent e.g. ethyl acetate. Alternatively when R_{11} is a diphenylmethyl group it may be removed by treatment with an acid such as trifluoroacetic acid.

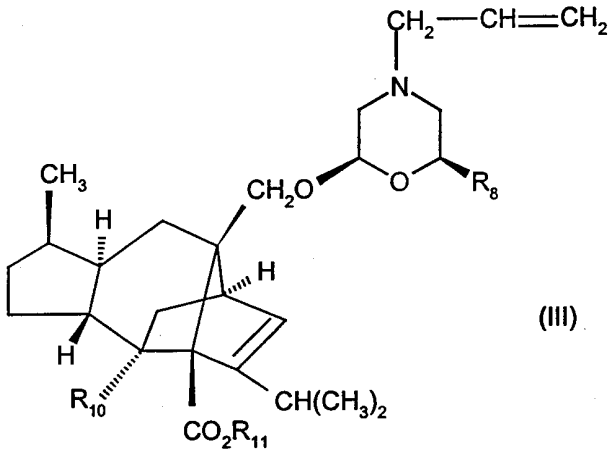
When R_{11} is a trimethylsilylethyloxymethyl group this may be cleaved by reaction with fluoride ions e.g. tetrabutylammonium fluoride in a suitable aprotic solvent such as an ether e.g. tetrahydrofuran.

When R_{10} is a protected formyl group this may be converted into the formyl group by conventional means. Thus if R_{10} is an acetal group it may be converted into the formyl group by treatment with an acid e.g. organic acid such as trifluoroacetic acid or an aqueous mineral acid e.g. aqueous hydrochloric acid.

Salts of compounds of formula (I) with inorganic or organic bases may be prepared by treating a solution or suspension of the compound of formula (I) e.g. a suspension in methanol with an equivalent amount of the base e.g sodium hydroxide optionally in a solvent e.g. water. The salts may be isolated by removal of the organic solvent followed by lyophilisation.

The compound of formula (II) may be prepared by the processes described and/or excemplified in WO99/58512 which is incorporated herein by reference.

Compounds of formula (II) may also be prepared by treating a compound of formula (III) wherein R_8 has the meanings defined in formula (I) and R_{10} and R_{11} have the meanings defined in formula (II):



(III)

with Wilkinson's catalysts $(Ph_3P)_3$ RhCl and diazabicylo [2,2,2]octane in aqueous ethanol and conveniently with heating.

Compounds of formula (III) may be prepared by the processes described and/or exemplified in WO99/58512.

The compound of formula (III) wherein R_{10} is CN may be prepared from the corresponding compound wherein R_{10} is CHO by reaction with hydroxylamine in a solvent such as toluene and then treatment of the resultant oxime with acetic anhydride and with heating.

Compounds of formula (I) or protected derivatives thereof may be converted into compounds of formula (I).

Thus compounds of formula (I) wherein R_9 is CN may be prepared from the corresponding compound of formula (I) wherein R_9 is CHO by reaction with

hydroxylamine in a solvent such as toluene and then treatment of the resultant oxime with acetic anhydride and with heating.

Metabolically labile esters of compounds of formula (I) may be prepared by reacting the corresponding acid or a base addition salt thereof e.g. the sodium salt with an activated derivative for the required alcohol e.g. a halide or a sulphonate derivative.

The following examples, which are non limiting illustrate the invention.

The intermediates and examples have been characterised by NMR determined on a Varian Unity 300 MH_z apparatus.

INTERMEDIATE 1

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]8a-[(6-deoxy-β-D-altropyranosyloxy)methyl]-4-(1,3-dioxolan-2yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

To a solution of [1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]8a-[(6-deoxy-β-D-altropyranosyloxy)methyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid (14 g) in 215 ml of a mixture dichloromethane:methanol v:v 20:1 was added dropwise 250ml of 0.35 N solution of diphenyldiazomethane in dichloromethane. After 30 minutes of stirring 1N HCl (180 ml) was added carefully and the mixture vigorously stirred until the purple colour disappeared. The two phases were partitioned and the organic layer washed with saturated aqueous sodium bicarbonate solution (500 ml) and dried over sodium sulphate. Elimination of the solvent gave a brown foamy crude which was purified by flash chromatography (silica gel), eluting firstly with dichloromethane, then with 10% methanol in dichloromethane. The materials thus obtained were dissolved in methanol (100 ml) and heated to 40°C. To the warm solutions were added ethylene glycol (50 ml), trimethyl orthoformate (6.5 ml) and *p*-toluenesulphonic acid (209 mg). Once the reaction was concluded the mixtures were cooled to room temperature and ethyl acetate (500 ml) was added onto them (TLC control Hexane:Acetone v:v 1:1).

Aqueous saturated sodium bicarbonate (50 ml) was added and the two phases partitioned. The organic layers were washed with water (500 ml) and brine (500 ml), then dried over sodium sulphate and concentrated to dryness. The foamy residues were dissolved in the minimal amount of diethyl ether and hexane was added dropwise until cloudy suspension was obtained, then they was cooled in the freezer overnight. The white solid thus obtained by precipitation was filtered off to obtain the desired product as white solid (85-90% overall yield from starting triol).

^{1}H-NMR ($CDCl_3$, ppm):
7.5-7.2 (m, 10H, Ph_2), 6.94 (s, 1H, $CHPh_2$), 5.83 (dd, 1H, H2, J=1.5 and 3.6 Hz), 5.07 (s, 1H, OCHO), 4.64 (d, 1H, H1', J=1.8 Hz), 4.05 (m, 2H, 8aCH_2+H2'), 3.90-3.65 (m, 8H, H3',+H4'+H5'+8aCH_2+OCH_2CH_2O), 2.64 (m, 1H, $CH(CH_3)_2$), 2.52 (t, 1H, H1, J= 3.9 Hz), 2.35, 2.27, 2.02 (3d, 3OH, J=2.4, 3.6 and 5.7 Hz).

INTERMEDIATE 2

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]8a-[(6-deoxy-β-D-mannopyranosyloxy) methyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H) carboxylic acid, diphenylmethyl ester was prepared using the procedure of Intermediate 1 but starting from [1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]8a-[(6-deoxy-β-D-mannopyranosyloxy) methyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H) carboxylic acid.

^{1}H-NMR ($CDCl_3$, ppm):
7.5-7.2 (m, 10H, Ph_2), 6.94 (s, 1H, $CHPh_2$), 5.82 (dd, 1H, H2, J=1.2 and 3.6 Hz), 5.08 (s, 1H, OCHO), 4.31 (d, 1H, H1', J=1.2 Hz), 4.07 (d, 1H, 8aCH_2, J=9.3 Hz), 3.94 (m, 1H, H3'), 3.9-3.75 (m, 4H, OCH_2CH_2O), 3.42 (m, 2H H2'+4'), 3.24 (m, 1H, H5'), 2.64 (m, 1H, $CH(CH_3)_2$), 2.54 (m, 2H, H1+OH), 2.36 (bs, 1H, OH), 2.33 (d, 1H, OH, J=2.4 Hz).

INTERMEDIATE 3

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]4-(1,3-dioxolan-2-yl)-8a-[((2R,4R)-4-methyl-3-oxa-pentanedial-2-yl)-oxymethyl]-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-

methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid diphenylmethylester

To a solution of intermediate 1 (23 g) in methanol (625 ml) was added solid sodium bicarbonate (5.62 g). To this suspension at 35°C was added dropwise with vigorous stirring a solution of sodium periodate (35.7g) in water (300 ml) over a period of 2h. Once the addition had been concluded, the suspension was stirred for 48h at 35° in the dark. The white solid was filtered off, the filter cake washed with methanol (200ml) and the combined filtrate and washing concentrated under vacuum to remove the methanol. Ethyl acetate (600 ml) was added and the two phases partitioned. The organic layer was washed twice with brine (2 x 100ml), dried over sodium sulphate and then the solvent removed under reduced pressure. After drying under vacuum the title compound (22.3g) was obtained as a white foam. This product was used in the reductive amination reactions described below without further purification.

Intermediate 3 may also be prepared using the above procedurre but using intermediate 2 as the starting material.

INTERMEDIATE 4

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)]-4-(1,3-dioxolan-2-yl)-8a-[(2R,6R)-(6-Methyl-morpholin-2-yl)-oxymethyl]-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid, ammonium salt.

To a solution of intermediate 3 (200 mg) in 20 mL of a solution of ammonia in methanol (0.1M), palladium (10%) on charcoal was added (10mg) under nitrogen. The mixture was shaken in a Parr apparatus (50 p.s.i.) for 24 h. The reaction was filtered and the solvent evaporated to dryness. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol 20:1 to give the title compound (131 mg) as a white solid.

^{1}H-NMR ($CDCl_3$, ppm):

5.95 (dd, 1H, H-2, J=1.2 and 3.3 Hz),4.62 (s, 1H, OCH_2O), 4.33 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.09 (d, 1H, $8aCH_a$, J=9.6 Hz), 4.13-4.05, 4.03-3.94 and

3.85-3.81 (3m, 4H, OCH_2CH_2O), 3.69 (d, 1H, 8aCH_b, J=9.6 Hz), 3.62 (m, 1H, H-6'), 2.91 (dd, 1H, H_a-3', J=2.1 and 12.0 Hz), 2.74 (dd, 1H, H_a-5', J= 2.1 and 12.3 Hz), 2.65 (t, 1H, H-1, J=3.9 Hz), 2.46 (dd, 1H, H_b-3', J=9.0 and 12.0 Hz), 2.40 (dd, 1H, H_b-5', J=10.2 and 12.3 Hz), 2.32 (m, 1H, $CH(CH_3)_2$).

INTERMEDIATE 5

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)- 6-methyl-4-allyl-morpholin-2-yl)-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid diphenylmethyl ester.

A mixture of Intermediate 3 (250 mg; 0.37 mmol), sodium cyanoborohydride (73 mg; 1.1 mmol), allylamine (52 mg; 0.92 mmol) and triethylamine (0.14 ml; 0.99 mmol) in dry acetonitrile (12.5 ml) was stirred at room temperature for 10 minutes. Glacial acetic acid (21 µl) was added and the resulting solution was stirred at room temperature for 1.5 hours. Afterwards, the reaction mixture was partitioned into ethyl acetate (10 ml) and water (10 ml). The organic layer was separated, washed with brine (2x10 ml), dried (sodium sulfate) and evaporated. The residue was purified by column chromatography using 1:2 ethyl acetate /hexane to afford the title compound (165 mg).

INTERMEDIATE 6

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-6-methyl-morpholin-2-yl)-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid diphenylmethyl ester.

A solution of Intermediate 5 (1.5 g; 2.2 mmol) in v/v 10/1 ethanol/water (20ml) is treated with Wilkinson's catalyst (0.140 g; 0.15 mmol) and diazabicyclo[2.2.2]octane (126 mg; 1.1 mmol) under argon for 30 minutes. The mixture is then heated under reflux for 4 hours. After this time, the reaction mixture is diluted with ethyl acetate, washed with water (1x 20 ml) and dried (sodium sulfate) to give a residue which is purified by column chromatography (5%v/v methanol in dichloromethane) to afford the title compound (1.1 g)

^{1}H-NMR (δ, ppm, $CDCl_3$):
7.26 to 7.44 (m, 10 H, 2x Ph), 6.94 (s, 1H, Ph_2CH), 5.84 (dd, 1H, H-2, J=0-9 and 3.3 Hz), 5.07 (s, 1H, OCHO), 4.38 (dd, 1H, H-2', J=2.1 and 8.7 Hz), 4.05 (AB system, 1H, 8a-CH2), 3.85 to 3.60 (m, 6H, OCH2CH2O + AB system + H-6'), 2.97 (m, 1H, CHN), 2.82 (m, 1H, CHN).

INTERMEDIATE 7

GENERAL METHOD

To a solution of intermediate 6 (case 3447) (100 mg, 0.15 mmol) in dichloromethane cooled to 0°C (ice-water bath), were added triethylamine (43μl) and the corresponding acyl chloride (0.2 mmol). The cooling bath was removed inmediatly after the adition of the reactive and the mixture allowed to warm to room temperature.
Filtration of triethylamine hydrochloride and elimination of the solvent gave a crude wich was purified by flash chromatography (silica gel), to afford the desired compound.

INTERMEDIATE 7a

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acetyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With acetyl chloride (15μl), and after purification with mixtures hexane:acetone v:v 15:1 to 7:1 the title compound (80 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.5-7.2 (m, 10H, Ph_2), 6.93, 6.92 (2s, 1H, $CHPh_2$), 5.83 (dd, 1H, H-2, J=0.9 and 1.2 Hz), 5.08 (s, 1H, OCHO), 4.49, 4.29 (2dm, 1H, H-3', J=12.9 Hz), 4.32, 4.24 (2dd, 1H, H-2', J=2.4 and 9.0 Hz), 4.06 (2d, 1H, 8aCH_2, J=9.3 Hz), 3.88-3.71 (m, 5H, OCH_2CH_2O, 8aCH_2), 3.56 (m, 2H, H-6', H-5'), 2.89 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.84 (dd, 0.5H, H-5', J=10.5 and 12.9 Hz), 2.66 (m, 1H,

$CH(CH_3)_2$), 2.43 (dd, 0.5H, H-3', J=9.0 and 12.9 Hz), 2.37 (dd, 0.5H, H-5', J=9.0 and 13.5 Hz), 2.09, 2.08 (2s, 3H, CH_3CO).

INTERMEDIATE 7b

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-pentanoyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With valeryl chloride (25 µl), and after purification with mixtures hexane:acetone v:v 10:1 to 5:1, the title compound (90 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.5-7.2 (m, 10H, Ph_2), 6.93, 6.92 (2s, 1H, $CHPh_2$), 5.83 (m, 1H, H-2), 5.08 (s, 1H, OCHO), 4.49, 4.35 (2m, 1H, H-3'), 4.3-4.2 (m, 1H, H-2'), 4.06 (d, 1H, 8aCH_2, J=9.0 Hz), 3.90-3.65 (m, 5H, OCH_2CH_2O, 8aCH_2), 3.55 (m, 2H, H-5', H-6'), 2.86 (dd, 0.5 H, H-3', J=8.4 and 12.9 Hz), 2.79 (dd, 0.5H, H-5', J=6.9 and 9.3 Hz), 2.64 (m, 1H, $CH(CH_3)_2$), 2.55 (m, 1H, H-1), 2.40 (m, 1H, H-5', H-3'), 2.30 (m, 2H, CH_2CO).

INTERMEDIATE 7c

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acryloyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With acryloyl chloride (17 µl), and after purification with mixtures hexane: ethyl acetate v:v 3:1 to 1:1 the title compound (105 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.46-7.26 (m, 10H, Ph_2), 6.92 (s, 1H, $CHPh_2$), 6.53 (m, 1H, $CH=CH_2$), 6.30 (m, 1H, $CH=CH_2$), 5.83 (m, 1H, H-2), 5.75 (m, 1H, $CH=CH_2$), 5.08 (s, 1H, OCHO), 4.51, 4.47 (2bd, 1H, H-3'), 4.28 (dd, 1H, H-2', J=2.7 and 6.0 Hz), 4.06 (d, 1H, H-

8a, J=9.0 Hz), 3.86-3.71 (m, 5H, OCH_2CH_2O, H-8a), 3.70 (m, 1H, H-5'), 3.57 (m, 1H, H-6'), 2.89 (m, 1H, $CH(CH_3)_2$), 2.52 (m, 2H, H-5', H-1).

INTERMEDIATE 7d

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Methoxyacetyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With methoxyacetyl chloride (15 µl), and after purification with mixtures hexane:ethyl acetate v:v 2:1 to 1:1 the title compound (100 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.46-7.26 (m, 10H, Ph_2), 6.93, 6.92 (2s, 1H, $CHPh_2$), 5.83 (m, 1H, H-2), 5.08 (s, 1H, OCHO), 4.45, 4.30 (2m, 1H, H-3'), 4.28 (m, 1H, H-2'), 4.09 (m, 3H, H-8a, CH_2OCH_3), 3.86-3.74 (m, 5H, OCH_2CH_2O, H-8a), 3.60 (m, 2H, H-5', H-6'), 3.42, 3.41 (2s, 3H, OCH_3), 2.86 (dd, 0.5H, H-3', J=8.4 and 12.6 Hz), 2.79 (dd, 0.5H, H-3', J=8.7 and 12.6 Hz), 2.64 (m, 1H, $CH(CH_3)_2$), 2.54 (m, 1H, H-1), 2.46 (dd, 0.5H, H-5', J=6.9 and 12.9 Hz), 2.42 (dd, 0.5H, H-5', J=10.8 and 12.9 Hz).

INTERMEDIATE 7e

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Fluorobenzoyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With 4-fluorobenzoyl chloride (19 µl), and after purification with mixtures hexane:ethyl acetate v:v 4:1 to 3:1, the title compound (120 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.45-7.26 (m, 12H, Ph_2, 2H-Ar), 7.10 (m, 2H, 2H-Ar), 6.92 (s, 1H, $CHPh_2$), 5.80 (m, 1H, H-2), 5.07 (s, 1H, OCHO), 4.60, 4.40 (2m, 1H, H-3'), 4.33 (m, 1H, H-2'),

4.03 (m, 1H, H-8a), 3.80 (m, 4H, OCH_2CH_2O), 3.78 (m, 2H, H-8a, H-5'), 3.60 (m, 1H, H-6'), 2.83 (m, 1H, H-3'), 2.64 (m, 2H, H-1, $CH(CH_3)_2$), 2.50 (m, 1H, H-5').

INTERMEDIATE 7f

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Benzoyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With benzoylchloride (16 µl), and after purification with mixtures hexane:ethyl acetate v:v 2:1 to 1:1 the title compound (74 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers, 50°C):
7.46-7.22 (m, 15H, H-Ar), 6.94 (s, 1H, $CHPh_2$), 5.79 (m, 1H, H-2), 5.07 (s, 1H, OCHO), 4.32 (m, 2H, H-3', H-2'), 4.04 (d, 2H, H-8a, J=9.0 Hz), 3.86-3.73 (m, 6H, OCH_2CH_2O, H-8a, H-5'), 3.63 (m, 1H, H-6'), 2.74 (m, 2H, H-3', H-5'), 2.64 (m, 1H, $CH(CH_3)_2$), 2.49 (m, 1H, H-1).

INTERMEDIATE 7g

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(4-Methoxybenzoyl), 6-methyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With 4-methoxybenzoyl chloride (20 µl), and after purification with mixtures hexane:ethyl acetate v:v 3:1 to 2:1 the title compound (100 mg) was obtained as a white foam (mixture of rotamers).

^{1}H-NMR ($CDCl_3$, ppm, two rotamers, 50°C):
7.46-7.22 (m, 1H, H-Ar), 6.92 (m, 3H, $CHPh_2$, 2H-Ar), 5.80 (m, 1H, H-2), 5.07 (s, 1H, OCHO), 4.33 (m, 1H, H-3'), 4.32 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.05 (m, 1H, H-5'), 4.04 (d, 1H, H-8a, J=9.0 Hz), 3.83 (s, 3H, OCH_3), 3.78 (m, 5H, OCH_2CH_2O, H-8a), 3.63 (m, 1H, H-6'), 2.73 (m, 2H, H-3', H-5'), 2.63 (m, 1H, $CH(CH_3)_2$), 2.50 (m, 1H, H-1).

INTERMEDIATE 7h

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-methylsulphonyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With methylsulphonyl chloride (14 µl), and after purification with mixtures hexane:ethyl acetate v:v 3:1, the title compound (90 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
7.44, 7.30 (2m, 10H, 2Ph), 6.92 (s, 1H, $CHPh_2$), 5.83 (dd, 1H, H-2, J=1.2 and 3.6 Hz), 5.08 (s, 1H, OCHO), 4.41 (dd, 1H, H-2', J=2.7 and 8.7 Hz), 4.07 (d, 1H, H-8a, J=9.0 Hz), 3.82 (m, 4H, OCH_2CH_2O), 3.77 (d, 1H, H-8a, J=9.0 Hz), 3.72 (m, 1H, H-6'), 3.66 (dm, 1H, H-3', J=11.1 Hz), 3.51 (dm, 1H, H-5', J=12.6 Hz), 2.76 (s, 3H, CH_3), 2.65 (m, 1H, $CH(CH_3)_2$), 2.52 (t, 1H, H-1, J=3.9 Hz), 2.43 (dd, 1H, H-3', J=8.7 and 11.4 Hz), 2.38 (dd, 1H, H-5', J=10.2 and 11.4 Hz).

INTERMEDIATE 7i

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-dimethylsulfamoyl) morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With dimethylsulfamoyl chloride (17 µl), and after purification with mixtures hexane:ethyl acetate v:v 1:1, the title compound (93 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
7.43, 7.28 (2m, 10H, Ph_2), 6.92 (s, 1H, $CHPh_2$), 5.84 (dd, 1H, H-2, J=1.2 and 3.6 Hz), 5.08 (s, 1H, OCHO), 4.36 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.05 (d, 1H, H-8a, J=9.0 Hz), 3.85 (m, 4H, OCH_2CH_2O), 3.76 (d, 1H, H-8a, J=9.0 Hz), 3.68 (m, 1H, H-6'), 3.58 (dm, 1H, H-3', J=11.7 Hz), 3.44 (dm, 1H, H-5', J=11.4 Hz),

2.82 (s, 6H, $2CH_3$), 2.64 (m, 1H, $CH(CH_3)_2$), 2.60 (dd, 1H, H-3', J=8.7 and 11.4 Hz), 2.57 (dd, 1H, H-5', J=8.7 and 11.4 Hz), 2.52 (t, 1H, H-1, J=3.9 Hz).

INTERMEDIATE 7j

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(4-Acetamidobenzene-sulphonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-(1,3-dioxolan-2-yl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid, diphenylmethyl ester.

With n-acetylsulfanilyl chloride (40 mg), and after purification with mixtures hexane:ethyl acetate v:v 2:1, the title compound (120 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):

7.68 (s, 4H, H-Ar), 7.43, 7.28 (2m, 10H, Ph_2), 6.93 (s, 1H, $CHPh_2$), 5.85 (d, 1H, H-2, J=3.3 Hz), 5.07 (s, 1H, OCHO), 4.41 (dd, 1H, H-2', J=2.7 and 8.7 Hz), 4.01 (d, 1H, H-8a, J=9.0 Hz), 3.80 (m, 4H, OCH_2CH_2O), 3.76 (d, 1H, H-8a, J=9.0 Hz), 3.70 (m, 1H, H-6'), 3.63 (dm, 1H, H-3', J=11.1 Hz), 3.49 (dm, 1H, H-5', J=10.5 Hz), 2.64 (m, 1H, $CH(CH_3)_2$), 2.50 (t, 1H, H-1, J=3.9 Hz), 2.21 (s, 3H, $COCH_3$), 2.05 (dd, 1H, H-3", J=8.7 and 11.1 Hz), 1.98 (dd, 1H, H-5', J=10.5 and 10.8 Hz).

INTERMEDIATE 8

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acetyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-(hydroxyimino methyl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

Hydroxylamine hydrochloride (140 mg) was added to a solution of Example 1a (320 mg) in dry toluene (5 ml) in the presence of triethylamine (0.25 ml). The reaction mixture was stirred 1 hour under reflux until a white precipitate appears. It was then concentrated and partitioned between 1 N hydrochloric acid (15 ml) and dichloromethane (15 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated.

The title compound (313 mg) was obtained as a white precipitate, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
7.81, 7.80 (2s, CH=N), 6.02 (d, 1H, H-2, J=3.3 Hz), 4.50, 4.34 (2d, 1H, H-3', J=13.8 Hz), 4.33, 4.28 (2dd, 1H, H-2', J=2.4 and 9.0 Hz), 4.11, 4.09 (2d, 1H, H-8a, J=9.3 Hz), 3.64, 3.59 (2d, 1H, H-8a, J=9.3 Hz), 3.68-3.49 (m, 2H, H-6', H-5'), 2.91 (dd, 0.5H, H-3', J=9.0 and 12.9 Hz), 2.85 (dd, 0.5H, H-5', J=10.5 and 13.2 Hz), 2.63 (t, 1H, H-1, J=3.6 Hz), 2.46 (dd, 0.5H, J=8.7 and 12.9 Hz), 2.38 (dd, 0.5H, H-5', J=10.8 and 13.2 Hz), 2.35 (m, 1H, C<u>H</u>$(CH_3)_2$), 2.11, 2.09 (2s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
176.0 (CHO), 169.6, 169.5 (CON), 156.8, 155.9 (C=N), 148.8, 148.6 (C-3), 130.4, 130.1 (C-2), 98.7, 98.2 (C-2'), 75.0, 74.7 (C-8a), 69.9 (C-6'), 51.4, 49.9, 46.4, 44.5 (C-3', C-5').

EXAMPLE 1
GENERAL METHOD

A solution of compounds obtained in Intermediate 7 (100 mg) in ethyl acetate (10 ml) was purged with nitrogen for 5 minutes and palladium 10% on charcoal (60% w/w) was added onto it. This suspension was shaken at room temperature under hydrogen (40 psi) in a Parr apparatus for 2.5 hours.
Filtration of catalyst and removal of the solvent, gave a crude wich was dissolved in tetrahydrofuran (10 ml). To this solution were added 1N HCl (5 ml). After completion the solution was diluted with water (15 ml) and extracted with ethyl acetate (3x15 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml) and dried over sodium sulphate. The solvent removed to dryness gave a crude wich was purified by preparative thin layer chromatography, eluting with mixtures of dichloromethane:methanol v:v 20:1. Extraction of appropriate fraction afforded the desired compound.

EXAMPLE 1a
[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acetyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

The Intermediate 7a (100 mg) gave with this method, 50 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.76, 9.74 (2s, 1H, CHO), 6.06 (bd, 1H, H-2, J=3.6 Hz), 4.52 (d, 0.5H, H-3', J=12.9 Hz), 4.40-4.32 (m, 1H, H-3', H-2'), 4.29 (dd, 0.5H, H-2', J=2.7 and 8.7 Hz), 4.13, 4.11 (2d, 1H, 8aCH_2, J=9.0 Hz), 3.65 (d, 0.5H, H-5', J=12.9 Hz), 3.60 (m, 1.5H, H-6', H-5'), 3.58, 3.52 (2d, 1H, 8aCH_2, J=9.0 Hz), 2.91 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.84 (dd, 0.5H, H-5', J=10.5 and 12.9 Hz), 2.67 (t, 1H, H-1, J=3.9 Hz), 2.47 (dd, 0.5H, H-3', J=8.7, 12.9 Hz), 2.37 (dd, 0.5H, H-5', J=10.5, 12.9 Hz), 2.33 (m, 1H, C<u>H</u>$(CH_3)_2$), 2.11, 2.01 (2s, 3H, CH_3).

EXAMPLE 1b

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-pentanoyl) morpholin-2-yl-oxymethyl]-4-(formyl)-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

The Intermediate 7b (100 mg) gave with this method 60 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.77, 9.74 (2s, 1H, CHO), 6.06 (dd, 1H, H-2, J=1.2 and 3.6 Hz), 4.53 (d, 0.5H, H-3', J=12.9 Hz), 4.40-4.32 (m, 1.5H, H-3', H-2'), 4.13, 4.11 (2d, 1H, 8aCH_2, J=9.0 Hz), 3.80-3.55 (m, 3H, H-5', H6', 8aCH_2), 2.88 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.84 (dd, 0.5H, H-5', J=11.1 and 13.2 Hz), 2.67 (t, 1H, H-1, J=3.9 Hz), 2.50-2.23 (m, 4H, H-5', H-3', CH_2CO, C<u>H</u>$(CH_3)_2$).

EXAMPLE 1c

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acryloyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methyl-ethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

In this reaction, the solution of Intermediate 7c (100 mg) in dichloromethane (10 ml) was treated with trifluoroacetic acid (200 µl).

After completion the solvent was removed to dryness and the crude was purified by preparative TLC, eluting with dichloromethane:methanol v/v 20:1. Extraction of the appropriate fraction afforded 50 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.65 (s, 1H, CHO), 6.50 (m, 1H, C<u>H</u>=CH_2), 6.32 (dm, 1H, CH=C<u>H</u>$_{2t}$, J=17.7 Hz), 6.06 (d, 1H, H-2, J=3.9 Hz), 5.74 (dm, 1H, CH=C<u>H</u>$_{2c}$, J=9.9 Hz), 4.59, 4.43 (2dm, 1H, H-3', J=12.6 Hz), 4.34 (dd, 1H, H-2', J=2.4 and 9.0 Hz), 4.17 (d, 1H, H-8a, J= 9.0 Hz), 3.85, 3.70 (2dm, 1H, H-5', J=11.4 Hz), 3.56 (m, 2H, H-6', H-8a), 2.90 (m, 1H, H-3'), 2.65 (m, 1H, H-1), 2.50 (m, 1H, H-5'), 2.34 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.6 (CHO), 175.6 (COOH), 168.8 (CON), 148.8 (C-3), 130.3 (C-2), 128.6 ($\underline{C}H_2$=CH), 127.2 (CH_2=$\underline{C}$H), 98.3 (C-2'), 73.9 (C-8a), 70.2 (C-6'), 50.8, 48.8, 46.8, 44.8 (C-3', C-5').

EXAMPLE 1d

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Methoxyacetyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

The Intermediate 7d (100 mg) gave with this method 65 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.71, 9.69 (2s, 1H, CHO), 6.06 (bd, 1H, H-2, J=3.0 Hz), 4.47, 4.33 (2m, 1H, H-3'), 4.32 (m, 1H, H-2'), 4.10 (m, 3H, H-8a, $\underline{C}H_2$-OCH_3), 3.57 (m, 3H, H-5', H-8a, H-6'), 3.42, 3.41 (2s, 3H, OCH_3), 2.87 (dd, 05H, H-3', J=8.7 and 13.2 Hz), 2.79 (dd, 0.5H, H-5', J=11.1 and 13.2 Hz), 2.67 (t, 1H, H-1, J=3.9 Hz), 2.50 (dd, 0.5H, H-3', J=8.7 and 12.6 Hz), 2.44 (dd, 0.5H, H-5', J=10.9 and 13.2 Hz), 2.33 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):

205.1 (CHO), 175.3 (COOH), 168.0 (CON), 148.5, 148.3 (C-3), 130.8, 130.5 (C-2), 98.4, 98.3 (C-2'), 74.1 (C-8a), 71.8 (CH_2-OCH_3), 70.1, 70.0 (C-6'), 59.0, 58.9 (OCH_3), 50.0, 48.1, 46.7, 44.7 (C-3', C-5').

EXAMPLE 1e

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(4-Fluorobenzoyl), 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

The Intermediate 7e gave with this method 70 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR (CD_3OD, ppm, two rotamers, 50°C):
9.78 (s, 1H, CHO), 7.47, 7.19 (2m, 4H, H-Ar), 6.01 (bs, 1H, H-2), 4.39 (dd, 1H, H-2', J=2.4 and 8.4 Hz), 3.95 (d, 1H, H-8a, J=9.0 Hz), 3.74 (d, 1H, H-8a, J=9.0 Hz), 3.68 (m, 3H, H-6', H-3', H-5'), 2.80 (m, 2H, H-3', H-1), 2.62 (m, 1H, H-5'), 2.32 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR (CD_3OD, ppm, two rotamers):
206.7 (CHO), 175.7 (COOH), 171.8 (CON), 150.1 (C-3), 131.4 (C-2), 130.7, 116.8, 116.5 (C-Ar), 99.5 (C-2'), 75.5 (C-8a), 71.0 (C-6').

EXAMPLE 1f

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Benzoyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

The Intermediate 7f (60 mg) gave with this method 40 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers, 50°C):
9.46 (s, 1H, CHO), 7.41 (m, 5H, H-Ar), 6.05 (m, 1H, H-2), 4.36 (m, 2H, H-3', H-2'), 4.12 (m, 1H, H-5'), 4.10 (d, 1H, H-8a, J=9.0 Hz), 3.64 (m, 1H, H-6'), 3.62 (d, 1H, H-8a, J=9.0 Hz), 2.75 (m, 2H, H-3', H-5'), 2.66 (m, 1H, H-1), 2.40 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
206.9 (CHO), 176.0 (COOH), 170.6 (CON), 149.2 (C-3), 135.2 (C-Ar hipso), 130.0 (C-2), 128.6, 127.1 (C-Ar), 98.6 (C-2'), 74.7 (C-8a), 70.2 (C-6').

EXAMPLE 1g

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(*p*-Methoxybenzoyl), 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

The Intermediate 7g (100 mg) gave with this method 49 mg of the title compound as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.75 (s, 1H, CHO), 7.37 (m, 2H, H-Ar), 6.93 (m, 2H, H-Ar), 6.06 (m, 1H, H-2), 4.41 (m, 1H, H-2'), 4.23 (d, 1H, H-8a, J=9.3 Hz), 3.90 (m, 1H, H-3'), 3.84 (s, 3H, OCH_3), 3.61 (m, 2H, H-5', H-6'), 3.52 (d, 1H, H-8a, J=9.3 Hz), 2.78 (m, 2H, H-3', H-5'), 2.58 (m, 1H, H-1), 2.34 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.1, 204.3 (CHO), 175.7, 175.3 (COOH), 170.6 (CON), 161.0 (C-Ar hipso), 148.4 (C-3), 130.7 (C-2), 129.3, 127.1, 113.8 (C-Ar), 98.4 (C-2'), 74.1 (C-8a), 70.2 (C-6'), 55.3 (OCH_3).

EXAMPLE 1h

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-methylsulphonyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

The Intermediate 7h (100 mg) gave with this method 65 mg of the title compound as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
9.69 (s, 1H, CHO), 6.08 (dd, 1H, H-2, J=1.2 and 3.3 Hz), 4.46 (dd, 1H, H-2', J=2.7 and 8.7 Hz), 4.13 (d, 1H, H-8a, J=9.3 Hz), 3.73 (m, 1H, H-6'), 3.69 (dm,

1H, H-3', J=11.7 Hz), 3.61 (d, 1H, H-8a, J=9.3 Hz), 3.52 (dm, 1H, H-5', J=10.8 Hz), 2.76 (s, 3H, CH_3), 2.66 (t, 1H, H-1, J=3.9 Hz), 2.44 (dd, 1H, H-3', J=8.7 and 11.1 Hz), 2.38 (dd, 1H, H-5', J=10.5 and 11.4 Hz), 2.33 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm):
205.0 (CHO), 175.6 (COOH), 148.4 (C-3), 130.7 (C-2), 98.4 (C-2'), 74.4 (C-8a), 70.6 (C-6'), 50.3, 48.2 (C-3', C-5').

EXAMPLE 1i

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-methylsulfamoyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

The product Intermediate 7i (100 mg) gave with this method 60 mg of the title compound as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
9.53 (s, 1H, CHO), 6.08 (d, 1H, H-2, J=3.6 Hz), 4.41 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.15 (d, 1H, H-8a, J=9.3 Hz), 3.67 (m, 1H, H-6'), 3.62 (dm, 1H, H-3', J=11.1 Hz), 3.59 (d, 1H, H-8a, J=9.3 Hz), 3.44 (dm, 1H, H-5', J=11.1 Hz), 2.82 (s, 6H, $2CH_3$), 2.65 (m, 1H, H-1), 2.55 (m, 2H, H-3', H-5'), 2.37 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm):
207.9 (CHO), 176.1 (COOH), 149.0 (C-3), 130.5 (C-2), 98.4 (C-2'), 74.6 (C-8a), 69.9 (C-6'), 51.0, 48.9 (C-3', C-5'), 38.2 (CH_3-N).

EXAMPLE 1j

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(4-Acetamidobenzene-sulphonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

The product Intermediate 7j (100 mg) gave with this method 65 mg of the title compound as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
9.60 (bs, 1H, NH), 7.72, 7.62 (2m, 4H, H-Ar), 6.03 (m, 1H, H-2), 4.40 (m, 1H, H-2'), 3.95 (d, 1H, H-8a, J=9.3 Hz), 3.63 (m, 2H, H-8a, H-6'), 3.61 (bd, 1H, H-3'), 3.45 (bd, 1H, H-5', J=10.8 Hz), 2.65 (m, 1H, H-1), 2.38 (m, 1H, $CH(CH_3)_2$), 2.16 (s, 1H, CH_3CO), 1.95 (m, 2H, H-3', H-5').

^{13}C-NMR ($CDCl_3$, ppm):
206.4 (CHO), 176.0 (COOH), 169.4 (NHCO), 149.0 (C-Ar hipso), 142.8 (C-3), 130.3 (C-2), 129.2 (C-Ar), 128.8 (C-Ar hipso), 119.2 (C-Ar), 98.5 (C-2'), 75.0 (C-8a), 69.3 (C-6'), 50.4, 48.4 (C-3', C-5').

EXAMPLE 2
GENERAL METHOD

To a solution of intermediate 4 (100 mg, 0.20 mmol) in dichloromethane (5 ml) were added trietylamine (50 µl) and the reactive (acyl chloride or isocyanate) (0.22 mmol). After 1 hour, filtration of triethylamine hydrochloride and elimination of the solvent gave a crude wich was treated with HCl 1N (3 ml) in tetrahydrofuran (6 ml) during 4 hours. After completion the solution was diluted with water (5 ml) and extracted with ethyl acetate (3x5 ml). The organic layer dried over magnesium sulphate, and the solvent removed to dryness gave a crude wich was purified by preparative thin layer chromatography, eluting with mixtures dichloromethane:methanol v:v 20:1 10:1. Extraction of the appropriate fraction afforded the desired compound.

EXAMPLE 2a

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-propanoyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

With propanoyl chloride (15 µl), the title compound (60 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):

9.64, 9.63 (2s, 1H, CHO), 6.07 (dd, 1H, H-2, J=1.2 and 3.3 Hz), 4.53, 4.37 (2d, 1H, H-3', J=12.0 Hz), 4.31 (dd, 1H, H-2', J=2.1 and 8.7 Hz), 4.17, 4.15 (2d, 1H, H-8a, J=9.3 Hz), 3.70, 3.52 (2d, 1H, H-5', J=11.8 Hz), 3.52 (m, 2H, H-8a, H-6'), 2.88 (dd, 0.5H, H-3', J=8.7 and 12.6 Hz), 2.80 (dd, 0.5H, H-5', J=8.7 and 11.4 Hz), 2.66 (t, 1H, H-1, J=3.9 Hz), 2.48 (dd, 0.5H, H-3', J=8.7 and 12.6 Hz).

EXAMPLE 2b

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Chloroacetyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

With chloroacetylchloride (16 µl), the title compound (50 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.71, 9.70 (2s, 1H, CHO), 6.07 (bd, 1H, H-2, J=3.3 Hz), 4.45 (dm, 0.5H, H-3', J=13.0 Hz), 4.42, 4.34 (2dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.30 (dm, 0.5H, H-3', J=12.9 Hz), 4.13 (d, 1H, H-8a, J=9.0 Hz), 4.06 (Absystem, 2H, CH_2Cl, J= 6.0 Hz), 3.75-3.55 (m, 3H, H-8a, H-6', H-5'), 2.97 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.90 (dd, 0.5H, H-5', J=10.5 and 13.2 Hz), 2.67 (m, 1H, H-1), 2.53 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.45 (dd, 0.5H, H-5', J=10.5 and 13.2 Hz), 2.33 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
204.9 (CHO), 174.9 (COOH), 165.5 (CON), 148.2 (C-3), 130.8, 130.7 (C-2), 98.1, 98.0 (C-2'), 74.1 (C-8a), 70.0, 69.9 (C-6'), 51.2, 49.3, 47.0, 44.9 (C-3', C-5'), 40.7 (CH_2-Cl).

EXAMPLE 2c

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Isopropyl-carbonyl), 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

With isobutyryl chloride (22 µl), the title compound (80 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.59 (s, 1H, CHO), 6.06 (d, 1H, H-2, J=3.3 Hz), 4.54, 4.36 (2m, 1H, H-3'), 4.31 (m, 1H, H-2'), 4.13 (d, 1H, H-8a, J=9.3 Hz), 3.84-3.56 (m, 3H, H-8a, H-6', H-5'), 2.86 (m, 1H, H-3'), 2.67 (m, 1H, H-1), 2.44 (m, 1H, H-5'), 2.36 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
206.4 (CHO), 178.3 (COOH), 175.8 (CON), 149.2 (C-3), 130.6, 130.2 (C-2), 98.7, 98.4 (C-2'), 74.4 (C-8a), 70.2 (C-6'), 50.6, 48.7, 46.7, 44.7 (C-3', C-5').

EXAMPLE 2d

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-*tert*-Butyl-acetyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With tert-butylacetyl chloride (30 µl), the title compound (83 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.66, 9.65 (2s, 1H, CHO), 6.06 (m, 1H, H-2), 4.60, 4.43 (2m, 1H, H-3'), 4.30 (m, 1H, H-2'), 4.14 (d, 1H, H-8a, J=9.3 Hz), 3.84 (m, 1H, H-5'), 3.62 (d, 1H, H-8a, J=9.3 Hz), 3.54 (m, 1H, H-6'), 2.86 (m, 1H, H-3'), 2.65 (m, 1H, H-1'), 2.40 (m, 1H, H-5').

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.6 (CHO), 170.7 (COOH), 148.5 (C-3), 130.7, 130.4 (C-2), 98.6, 98.3 (C-2'), 74.2 (C-8a), 70.1, 70.0 (C-6'), 51.7, 49.7, 46.3, 44.6 (C-3', C-5').

EXAMPLE 2e

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Ethylmalonyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With malonyl chloride (30 µl), the title compound (40 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.64, 9.63 (2s, 1H, CHO), 6.07 (m, 1H, H-2), 4.53, 4.37 (2dm, 1H, H-3', J=13.8 Hz), 4.33, 4.31 (2d, 1H, H-8a, J=9.3 Hz), 4.20 (2q, 2H, OCH_2, J=7.2 and 14.4 Hz), 4.11 (m, 2H, H-2', J=8.7 Hz), 3.60 (m, 3H, H-5', H-8a, H-6'), 3.48 (AB system, 2H, $COCH_2CO$, J=4.8 Hz), 2.92 (dd, 0.5H, H-3', J=9.0 and 12.9 Hz), 2.87 (dd, 0.5H, H-5', J=10.5 and 13.2 Hz), 2.66 (m, 1H, H-1), 2.50 (dd, 0.5H, H-3', J=9.0 and 13.2 Hz), 2.40 (dd, 0.5H, H-5', J=10.8 and 13.5 Hz), 2.34 (m, 1H, $CH(CH_3)_2$), 1.28 (2t, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
206.0 (CHO), 175.2 (COOH), 167.3 (COO), 164.7 (CON), 148.8, 148.7 (C-3), 130.7, 130.5 (C-2), 98.4, 98.1 (C-2'), 74.3 (C-8a), 69.9 (C-6'), 61.7 (OCH_2), 51.4, 49.5, 46.8, 44.8 (C-3', C-5'), 41.2 (CH_2CO).

EXAMPLE 2f

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-phenylacetyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With phenylacetyl chloride (29 µl), the title compound (50 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.56, 9.54 (2s, 1H, CHO), 7.36-7.20 (m, 5H, H-Ar), 6.06, 5.93 (2d, 1H, H-2, J=2.7 Hz), 4.55 (d, 0.5H, H-3', J=13.2 Hz), 4.40 (d, 0.5H, H-3', J=13.8 Hz), 4.24 (dd, 0.5H, H-2', J=2.4 and 8.7 Hz), 4.13, 3.99 (2d, 1H, H-8a, J=9.3 Hz), 3.90 (dd, 0.5H, H-2', J=1.8 and 8.7 Hz), 3.82 (d, 0.5H, H-5', J=13.2 Hz), 3.68 (s, 2H, $COCH_2$), 3.57 (d, 0.5H, H-5', J=13.5 Hz), 3.52, 3.41 (2d, 1H, H-8a, J=9.3 Hz), 3.50, 3.25 (2m, 1H, H-6'), 2.83 (dd, 0.5H, H-3', J=8.4 and 12.6 Hz), 2.75 (dd, 0.5H, H-5', J=10.8 and 13.5 Hz), 2.64 (m, 1H, H-1), 2.50-2.33 (m, 1H, H-3', H-5').

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
206.4 (CHO), 175.8 (COOH), 169.9 (CON), 148.9, 148.7 (C-3), 134.8, 134.6 (C-Arhipso), 130.6, 130.3 (C-2), 128.6, 128.4, 126.9 (C-Ar), 98.4, 98.2 (C-2'), 74.4 (C-8a), 69.9 (C-6'), 51.1, 49.2, 46.7, 44.8 (C-3', C-5').

EXAMPLE 2h

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Cyclohexyl-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With cyclohexylcarbonyl chloride (29 µl), the title compound (52 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers, 50°C):
9.72 (s, 1H, CHO), 6.06 (d, 1H, H-2, J=3.3 Hz), 4.54, 4.38 (2dm, 1H, H-3'), 4.31 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.22 (d, 1H, H-8a, J=9.3 Hz), 3.58 (m, 3H, H-8a, H-5', H-6'), 2.83 (m, 1H, H-3'), 2.61 (m, 1H, H-1), 2.37 (m, 2H, H-3', C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.5 (CHO), 175.0 (COOH), 164.0 (CON), 148.4, 148.3 (C-3), 130.7, 130.4 (C-2), 98.6, 98.4 (C-2'), 74.1 (C-8a), 70.3, 70.1 (C-6'), 50.5, 48.6, 46.6, 44.5 (C-3', C-5').

EXAMPLE 2i

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-(3,4,5-trimethoxy-benzoyl))morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With 3,4,5-trimethoxy-benzoyl chloride (51 mg), the title compound (75mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers, 50°C):
9.67 (s, 1H, CHO), 6.62 (s, 2H, H-Ar), 6.05 (m, 1H, H-2), 4.40 (m, 1H, H-2'), 4.30 (m, 1H, H-3'), 4.20 (d, 1H, H-8a, J=9.0 Hz), 3.87 (s, 9H, $3CH_3O$), 3.72 (m,

1H, H-5'), 3.63 (m, 1H, H-6'), 3.55 (d, 1H, H-8a, J= 9.0 Hz), 2.78 (m, 2H, H-3', H-5'), 2.61 (m, 1H, H-1), 2.37 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.6 (CHO), 170.4 (COOH), 153.4 (CON), 148.6 (C-3), 139.6 (C-Arhipso), 130.6 (C-2), 130.4 (C-Arhipso), 104.5 (C-Ar), 98.4 (C-2'), 74.2 (C-8a), 70.3 (C-6'), 56.3 (OCH_3).

EXAMPLE 2j

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Methoxy-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With methylchloroformate (10 µl), the title compound (63 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
9.74 (s, 1H, CHO), 6.07 (dd, H-2, J=1.2 and 3.6 Hz), 4.32 (dd, 1H, H-2', J=2.7 and 9.0 Hz), 4.16 (d, 1H, H-8a, J=9.6 Hz), 4.5-3.8 (m, 2H, H-3', H-5'), 3.71 (s, 3H, OCH_3), 3.56 (m, 1H, H-6'), 3.54 (d, 1H, H-8a, J=9.6 Hz), 2.65 (m, 1H, H-1), 2.50 (m, 2H, H-3', H-5'), 2.32 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm):
204.8 (CHO), 175.1 (COOH), 155.8 (CON), 148.2 (C-3), 130.7 (C-2), 98.3 (C-2'), 73.9 (C-8a), 70.1 (C-6'), 52.9 (OCH_3), 48.8, 46.5 (C-3', C-5').

EXAMPLE 2k

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Isopropenyloxy-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With isopropenyl chloroformate (13 µl), the title compound (60 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):

9.59 (s, 1H, CHO), 6.07 (d, 1H, H-2, J=3.0 Hz), 4.68 (bs, 2H, CH_2=), 4.36 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.14 (d, 1H, H-8a, J=9.6 Hz), 4.12-3.81 (m, 2H, H-3', H-5'), 3.57 (m, 2H, H-6', H-8a), 2.66 (m, 1H, H-1), 2.60 (m, 2H, H-3', H-5'), 2.36 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm):
205.0 (CHO), 176.0 (COOH), 153.1 (CON), 148.3 (C-3), 136.7 (<u>C</u>=CH_2), 130.7 (C-2), 101.8 (C=<u>C</u>H_2), 98.4 (C-2'), 74.0 (C-8a), 70.0 (C-6').

<u>EXAMPLE 2l</u>

<u>[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Ethyloxallyl, 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.</u>

With ethyloxallylchloride (24 µl), the <u>title compound</u> (90 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.67, 9.66 (2s, 1H, CHO), 6.07 (m, 1H, H-2), 4.45-4.25 (m, 4H, OCH_2, H-3', H-8a), 4.14 (m, 1H, H-2'), 3.62 (m, 2H, H-8a, H-6'), 3.58, 3.46 (2d, 1H, H-5'), 2.92 (m, 1H, H-3'), 2.65 (m, 1H, H-1), 2.54 (m, 1H, H-5'), 2.34 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.3, 205.2 (CHO), 175.6 (COOH), 162.2, 160.3 (2CO), 148.5, 148.4 (C-3), 130.8, 130.6 (C-2), 98.0 (C-2'), 74.4, 74.2 (C-8a), 70.1, 69.7 (C-6'), 62.4 (OCH_2), 50.8, 48.9 (C-3', C-5').

<u>EXAMPLE 2m</u>

<u>[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Furane-2-carbonyl), 6-methyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.</u>

With furane-2-carbonyl chloride (75 mg) (previously prepared refluxing furane-2-carboxylic acid with thionyl chloride), the <u>title compound</u> (40 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.46 (s, 1H, CHO), 7.50 (m, 1H, H-Ar), 7.03 (m, 1H, H-Ar), 6.50 (m, 1H, H-Ar), 6.07 (bd, 1H, H-2, J=2.7 Hz), 4.45 (m, 2H, H-3', H-5'), 4.37 (dd, 1H, H-2', J=3.0 and 8.4 Hz), 4.07 (d, 1H, H-8a, J= 9.3 Hz), 3.64 (m, 2H, H-8a, H-6'), 2.80 (m, 2H, H-3', H-5'), 2.71 (m, 1H, H-1), 2.37 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
207.4 (CHO), 176.4 (COOH), 159.2 (CON), 149.3 (C-3), 147.5 (C-Arhipso), 143.9 (C-Ar), 130.3 (C-2), 117.0, 111.4 (C-Ar), 98.6 (C-2'), 74.7 (C-8a), 70.1 (C-6').

EXAMPLE 2n

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-(thiophene-2-carbonyl))morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With thiophene-2-carbonyl chloride (65 mg) (previously prepared refluxing thiophene-2-carboxylic acid with thionyl chloride), the title compound (52 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.48 (s, 1H, CHO), 7.48 (m, 1H, H-Ar), 7.30 (m, 1H, H-Ar), 7.06 (m, 1H, H-Ar), 6.05 (bd, 1H, H-2, J=2.7 Hz), 4.39 (dd, 1H, H-2', J=2.1 and 8.7 Hz), 4.13 (m, 2H, H-3', H-5'), 4.10 (d, 1H, H-8a, J=9.3 Hz), 3.66 (m, 1H, H-6'), 3.62 (d, 1H, H-8a, J=9.3 Hz), 2.85 (m, 2H, H-3', H-5'), 2.69 (m, 1H, H-1), 2.37 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.2 (CHO), 177.8 (COOH), 163.7 (CON), 148.6, 148.4 (C-3), 136.5 (C-Arhipso), 130.7 (C-2), 129.3, 129.2, 126.8 (C-Ar), 98.7, 98.2 (C-2'), 73.9 (C-8a), 70.2 (C-6').

EXAMPLE 2o

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Isoxazole-5-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With isoxazole-5-carbonyl chloride (25 µl), the title compound (90 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.61 (s, 1H, CHO), 8.33 (m, 1H, H-Ar), 6.08 (m, 1H, H-2), 4.55 (d, 0.5H, H-3', J=12.9 Hz), 4.40 (m, 1.5H, H-3', H-2'), 4.15 (d, 0.5H, H-5', J=13.8 Hz), 4.11 (d, 1H, H-8a, J=9.3 Hz), 3.99 (d, 0.5H, H-5', J=13.9 Hz), 3.66 (m, 1H, H-6'), 3.65 (d, 1H, H-8a, J=9.3 Hz), 3.05 (dd, 0.5H, H-3', J=8.7 and 13.5 Hz), 2.98 (dd, 0.5H, H-5', J=10.8 and 13.5 Hz), 2.68 (m, 2H, H-3', H-5', H-1), 2.34 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.8 (CHO), 175.7 (COOH), 163.3 (CON), 156.9 (C=N), 150.2 (C-Ar), 148.6 (C-3), 130.7 (C-2), 108.3 (C-Ar), 98.2 (C-2), 74.5, 74.2 (C-8a), 70.3, 69.7 (C-6'), 51.4, 49.4, 47.6, 45.7 (C-3', C-5').

EXAMPLE 2p

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Benzo(b)thiophene-2-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With benzo(b)thiophene-2-carbonylchloride (50 mg), the title compound (85 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.70 (s, 1H, CHO), 7.85 (m, 2H, H-Ar), 7.50 (s, 1H, S-C=C<u>H</u>), 7.42 (m, 2H, H-Ar), 6.06 (m, 1H, H-2), 4.42 (m, 1H, H-2'), 4.20 (m, 1H, H-3'), 4.16 (d, 1H, H-8a, J=9.6 Hz), 3.72 (m, 1H, H-5'), 3.68 (m, 1H, H-6'), 3.58 (d, 1H, H-8a, J=9.6 Hz), 2.87 (m, 2H, H-5', H-3'), 2.65 (m, 1H, H-1), 2.32 (m, 1H, C<u>H</u>$(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
204.9 (CHO), 174.7 (COOH), 164.1 (CON), 148.3 (C-3), 140.2 (C-5), 138.5, 136.0 (C-Arhipso), 130.8 (C-2), 126.0, 125.7, 124.9, 124.7, 122.4 (C-Ar), 98.2 (C-2'), 74.0 (C-8a), 70.3 (C-6').

EXAMPLE 2q

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl, 4-nicotinoyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With nicotinoyl chloride (60 µl), the title compound (80 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.67 (s, 1H, CHO), 8.69 (m, 2H, H-Ar), 7.80 (m, 1H, H-Ar), 7.40 (m, 1H, H-Ar), 6.06 (m, 1H, H-2), 4.40 (m, 1H, H-2'), 4.13 (d, 1H, H-8a, J=9.0 Hz), 4.00 (m, 1H, H-3'), 3.69 (m, 2H, H-5', H-6'), 3.63 (d, 1H, H-8a, J=9.0 Hz), 2.79 (m, 2H, H-3', H-5'), 2.66 (m, 1H, H-1), 2.38 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.5 (CHO), 174.6 (COOH), 167.7 (CON), 148.5 (C-3), 147.6, 136.0, 131.4 (C-Ar), 130.7 (C-2), 124.0 (C-Ar), 98.6 (C-2'), 74.5 (C-8a), 70.5 (C-6').

EXAMPLE 2r

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(4-Methyl-2-phenyl,1,2,3-triazole-5-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With 4-methyl-2-phenyl-1,2,3-triazole-5-carbonyl chloride (27 mg), the title compound (85 mg) was obtained as a white foam, mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
9.70 (1H, s, CHO), 8.00 (m, 2H, H-Ar), 7.49 (m, 2H, H-Ar), 7.38 (m, 1H, H-Ar), 6.10, 6.05 (2d, 1H, H-2, J=3.0 Hz), 4.69, 4.57 (2dm, 1H, H-3', J=12.6 Hz), 4.47

(m, 2H, H-2', H-5'), 4.19, 4.15 (2d, 1H, H-8a, J=9.0 Hz), 3.73 (m, 1H, H-6'), 3.60 (d, 1H, H-8a, J=9.0 Hz), 3.05 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.97 (dd, 0.5H, H-5', J=10.5 and 13.5 Hz), 2.67 (m, 2H, H-1, H-3', H-5'), 2.54 (s, 3H, CH_3), 2.30 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
205.3 (CHO), 174.8 (COOH), 161.3 (CON), 148.6, 148.4 (C-3), 140.1, 139.3 (C=N), 130.8, 130.6 (C-2), 129.4, 127.9, 118.7 (C-Ar), 98.7, 98.4 (C-2'), 74.0 (C-8a), 70.7, 70.1 (C-6'), 52.2, 50.1, 46.5, 45.3 (C-3', C-5').

EXAMPLE 2s

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl,4-phenylsulphonyl) morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

With phenylsulphonyl chloride (25 µl), the title compound (70 mg) was obtained as a white foam.

^{1}H-NMR ($CDCl_3$, ppm):
9.43 (s, 1H, CHO), 7.73, 7.56 (2m, 5H, H-Ar), 6.07 (m, 1H, H-2), 4.45 (dm, 1H, H-2', J=8.7 Hz), 4.06 (d, 1H, H-8a, J=9.6 Hz), 3.70 (m, 2H, H-6', H-3'), 3.63 (d, 1H, H-8a, J=9.6 Hz), 3.51 (d, 1H, H-5', J=10.5 Hz), 2.66 (m, 1H, H-1), 2.37 (m, 1H, $CH(CH_3)_2$).

^{13}C-NMR ($CDCl_3$, ppm):
207.2 (CHO), 176.2 (COOH), 149.5 (C-3), 135.0 (C-Arhipso), 133.0 (C-2), 130.1, 129.1, 127.6 (C-Ar), 98.6 (C-2'), 75.4 (C-8a), 69.4 (C-6'), 50.4, 48.5 (C-3', C-5').

EXAMPLE 2t

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-(Ethylamino-carbonyl), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

With ethylisocyanate (16 µl), the title compound (40 mg) was obtained as a white foam.

^{1}H-NMR (CD_3OD, ppm):
9.79 (s, 1H, CHO), 6.03 (dd, 1H, H-2, J=1.2 and 3.6 Hz), 4.31 (dd, 1H, H-2', J=2.4 and 8.7 Hz), 3.98 (d, 1H, H-8a, J=9.6 Hz), 3.86 (dm, 1H, H-3', J=11.4 Hz), 3.74 (d, 1H, H-8a, J=9.6 Hz), 3.73 (dm, 1H, H-5', J=12.6 Hz), 3.60 (m, 1H, H-6'), 3.17 (q, 2H, NH-CH_2, J=7.5 and 14.7 Hz), 2.67 (t, 1H, H-1, J=3.9 Hz), 2.52 (dd, 1H, H-3', J=8.4 and 12.6 Hz), 2.45 (dd, 1H, H-5', J=10.8 and 12.9 Hz), 2.35 (m, 1H, C$H(CH_3)_2$).

^{13}C-NMR (CD_3OD, ppm):
207.5 (CHO), 176.4 (COOH), 159.9 (CON), 150.7 (C-3), 131.1 (C-2), 100.0 (C-2'), 75.9 (C-8a), 71.0 (C-6'), 49.9, 48.0 (C-3', C-5').

EXAMPLE 2u

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(6-Methyl-4-(phenylamino-carbonyl)), 6-methyl)morpholin-2-yl-oxymethyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-*s*-indacene-3a(1H)-carboxylic acid.

With phenylisocyanate (20 µl), the title compound (45 mg) was obtained as a white foam.

^{1}H-NMR (CD_3OD, ppm):
9.85 (s, 1H, CHO), 7.34, 7.24, 7.01 (3m, 5H, H-Ar), 5.98 (dd, 1H, H-2, J=1.2 and 3.3 Hz), 4.39 (dd, 1H, H-2', J=2.7 and 8.7 Hz), 4.08 (d, 1H, H-8a, J=9.6 Hz), 4.02 (dm, 1H, H-3', J=12.9 Hz), 3.92 (dm, 1H, H-5', J=12.6 Hz), 3.81 (d, 1H, H-8a, J=9.6 Hz), 3.68 (m, 1H, H-6'), 2.65 (m, 2H, H-3', H-1), 2.59 (dd, 1H, H-5', J=10.5 and 13.2 Hz), 2.43 (m, 1H, C$H(CH_3)_2$).

^{13}C-NMR (CD_3OD, ppm):
208.9 (CHO), 177.7 (COOH), 157.9 (CON), 151.9 (C-3), 140.7 (C-Arhipso), 130.5 (C-2), 129.5, 124.2, 122.2 (C-Ar), 100.0 (C-2'), 76.6 (C-8a), 71.0 (C-6'), 46.3, 44.4 (C-3', C-5').

EXAMPLE 3

[1R-(1α,3aβ,4β,4aβ,7β,7aα,8aβ)] 8a-[(2R,6R)-(4-Acetyl, 6-methyl)morpholin-2-yl-oxymethyl]-4-cyano-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-1,4-methano-s-indacene-3a(1H)-carboxylic acid.

Acetic anhydride (5 ml) was added to Intrmediate 8 (100 mg) and the mixture was stirred at 90°C for 2 hours. Crude reaction mixture was concentrated under vacuum and coevaporated with toluene. The residue thus obtained was chromatographed on silica using 2% methanol in dichloromethane to afford the title compound (49 mg), mixture of rotamers.

^{1}H-NMR ($CDCl_3$, ppm, two rotamers):
6.16 (d, 1H, H-2, J=3.3 Hz), 4.50, 4.35 (2dm, 1H, H-3', J=12.3 Hz), 4.33, 4.27 (2dd, 1H, H-2', J=2.4 and 8.7 Hz), 4.03, 4.01 (2d, 1H, H-8a, J=9.3 Hz), 3.67, 3.61 (2d, 1H, H-8a, J=9.3 Hz), 3.56 (m, 1.5H, H-6, H-5'), 3.52 (dm, 0.5H, H-5', J=12.3 Hz), 2.89 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.84 (dd, 0.5H, H-5', J=10.5 and 13.2 Hz), 2.71 (m, 1H, H-1), 2.67 (m, 1H, $CH(CH_3)_2$), 2.44 (dd, 0.5H, H-3', J=8.7 and 12.9 Hz), 2.37 (dd, 0.5H, H-5', J=10.5 and 13.0 Hz), 2.11, 2.09 (2s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, ppm, two rotamers):
174.5 (COOH), 169.7, 169.6 (CON), 150.0, 149.7 (C-3), 131.8, 131.4 (C-2), 123.9 (C≡N), 98.7, 98.2 (C-2'), 74.8, 74.5 (C-8a), 69.8 (C-6'), 51.3, 49.5, 46.4, 44.6 (C-3', C-5').

Pharmacy Examples

1. Conventional oral tablet

Drug substance	100 mg
Microcrystalline cellulose	160 mg
Crosscarmellose sodium	20 mg
Magnesium stearate	5 mg

The drug substance is blended with microcrystalline cellulose, crosscarmellose sodium and magnesium stearate, then compressed into tablets.

2. Conventional Capsule

Drug substance	100 mg
Lactose	200 mg
Magnesium stearate	2 mg

The drug substance is blended with the lactose and the magnesium stearate and then filled into appropriate capsules.

Anti-Fungal Activity

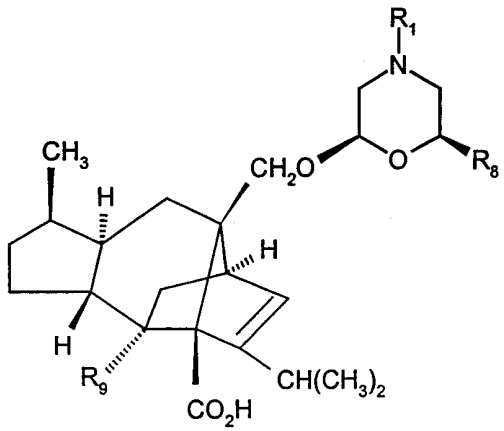
Compounds of formula (I) have been tested for anti-fungal activity in a standard *in vitro* screen and the minimum inhibiting concentrates (MIC;µg/ml) determined for each compound against a variety of clinically relevant pathogens. The results obtained with representative compounds of the invention are given below:

Example No.
MIC'S µg/ml

ORGANISM	1b	1g	2n	2p
C.albicans 4711E	0.06	0.50	0.12	0.12
C.albicans CL-236	NT	0.50	0.50	0.0015
C.tropicalis 2808E	0.25	0.50	0.50	0.50
C.pseudotropocalis 2371E	0.12	0.50	0.25	0.008

CLAIMS

1. A compound of formula (I),



(I)

and physiologically acceptable salts and or metabolically labile derivatives thereof, wherein R_1 represents a group selected from CXR_2, $CXOR_3$, $CONHR_4$ or SO_2R_5;

X is oxygen or sulphur;

R_2 is a group selected from C_{1-6} straight or branched chain alkyl, C_{2-6} straight or branched chain alkenyl, C_{2-6} straight or branched chain alkynyl, C_{1-4} straight or branched chain alkyl substituted by a group selected from (C_{1-4}alkoxy, hydroxy, halogen, C_{1-4}alkoxycarbonyl, carboxy or optionally substituted phenyl), optionally substituted phenyl, or optionally substituted 5 or 6 membered heteroaryl group or optionally substituted C_{5-7} cycloalkyl or C_{1-6} alkoxycarbonyl, R_3 is a group selected from C_{1-6} straight or branched alkyl, C_{2-6} straight or branched alkenyl or alkynyl or C_{1-4} straight or branched alkyl substituted by a group selected from C_{1-4}alkoxy, hydroxy, halogen, carboxy, C_{1-4} alkoxycarbonyl or optionally substituted phenyl; R_4 represents C_{1-6} straight or branched alkyl, or optionally substituted phenyl; R_5 represents C_{1-6} straight or branched alkyl, optionally substituted phenyl or the group NR_6R_7 wherein R_6 and R_7 independently represent hydrogen or C_{1-4} straight or branched alkyl;

R_8 represents a group selected from hydrogen, C_{1-6} straight or branched chain alkyl, C_{3-6} straight or branched chain alkenyl, optionally substituted phenyl or C_{1-4} alkyl substituted with a group selected from C_{1-4}alkoxy, hydroxy, acyloxy, alkoxy

carbonyl or aryloxycarbonyl, and R_9 represents a group selected from formyl or cyano.

2. A compound as claimed in claim 1 wherein R_9 is formyl.

3. A compound is claimed in claim 1 and or claim 2 wherein R_8 is methyl.

4. A compound as claimed in claims 1 to 3 wherein R_1 is a group selected from CXR_2 (wherein X is oxygen and R_2 is a group selected from C_{1-6} alkyl, C_{1-4} alkyl substituted by methoxy, C_{1-4} alkyl substituted by optionally substituted phenyl, C_{1-4} alkyl substituted by C_{1-4} alkoxycarbonyl) $CXOR_3$ (wherein X is oxygen and R_3 is C_{1-6} alkyl or C_{2-6} alkenyl), $CONHR_4$ wherein (R_4 is C_{1-6} alkyl or optionally substituted phenyl) or SO_2R_5 (wherein R_5 is C_{1-6} alkyl, optionally substituted phenyl or dialkyl amino).

5. A compound as claimed in any of claims 1 to 3 wherein R_1 is the group CXR_2 or $CXOR_3$ and X is oxygen.

6. A pharmaceutical composition comprising a compound as claimed in any claim 1 to 5 in admixture with one or more physiologically acceptable carriers or excipients.

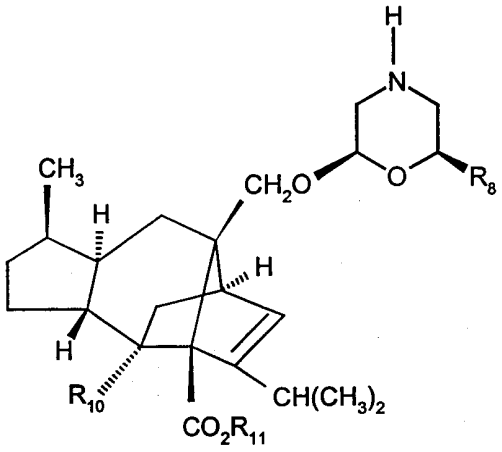
7. A compound as claimed in any of claims 1 to 5 for use in therapy.

8. The use of a compound as claimed in any of the claims 1 to 5 in the manufacture of a medicament for the treatment or prevention or preventive of fungal or protozoal infections.

9. A method of treatment of the human or non-human animal body to prevent or treat fungal and or protozoal diseases which method comprises administering to said body an effective amount of a compound claimed in any of claims 1 to 5.

10. A process for the preparation of compounds of formula (I), which comprises:

a) reacting a compound of formula (II) wherein R_8 has the meaning given in formula 1, R_{10} is cyano, formyl, or a protected formyl group and R_{11} is hydrogen, a carboxyl protecting or a cation of a salt,



(II)

with a compound capable of introducing the group R_1 followed where necessary or desired by removal of one or more protecting groups and isolation of the compound in the form of the free acid or a salt thereof;

b) a process for the preparation of formula (I) wherein R_9 is CN which comprises reacting from the corresponding compound of formula (I) wherein R_9 is CHO with hydroxylamine and then treating of the resultant oxime with acetic anhydride and heating.