



WATERSOLUBLE AZOLE ANTIFUNGALS

The present invention is concerned with novel water-soluble broad-spectrum azole antifungals as well as the antifungally active precursors thereof.

10 Systemic fungal infections in man are relatively rare in temperate countries and many of the fungi that can become pathogenic normally live commensally in the body or are common in the environment. However, the past few decades have witnessed an increasing incidence of numerous life-threatening systemic fungal infections world-wide and these now represent a major threat to many susceptible patients, particularly those
15 already hospitalized. Most of the increase can be attributed to improved survival of immunocompromised patients and the chronic use of antimicrobial agents. Moreover, the flora typical of many common fungal infections is also changing and this is presenting an epidemiological challenge of increasing importance. Patients at greatest risk include those with impaired immune functioning, either directly as a result of
20 immunosuppression from cytotoxic drugs or HIV infection, or secondary to other debilitating diseases such as cancer, acute leukaemia, invasive surgical techniques or prolonged exposure to anti-microbial agents. The most common systemic fungal infections in man are candidosis, aspergillosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and cryptococcosis.

25 Antifungals such as ketoconazole, itraconazole and fluconazole are being increasingly employed for the treatment and prophylaxis of systemic fungal infections in immunocompromised patients. However, concern about fungal resistance to some of these agents, especially the more narrow spectrum ones, e.g. fluconazole, is growing.
30 Worse still, it is recognized in the medical world that about 40% of the people suffering from severe systemic fungal infections are hardly able, or not at all to receive medication via oral administration. This inability is due to the fact that such patients are in coma or suffer from severe gastroparesis. Hence the use of insoluble or sparingly soluble antifungals such as itraconazole or saperconazole, that are difficult to administer
35 intravenously, is heavily impeded.

Consequently, there is a need for new antifungals, preferably broad-spectrum antifungals, against which there is no existing resistance and which can be administered



intravenously. Preferably the antifungal should also be available in a pharmaceutical composition suitable for oral administration. This enables the physician to continue treatment with the same drug after the patient has recovered from his condition which required intravenous administration of said drug.

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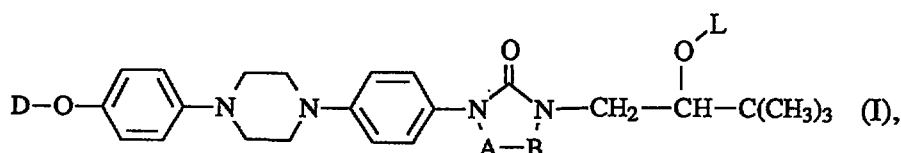
US-4,267,179 discloses heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxymethyl-1,3-dioxolan-2-yl)-methyl-1H-imidazoles and 1H-1,2,4-triazoles useful as antifungal and antibacterial agents. Said patent encompasses itraconazole, which is now available as a broadspectrum antifungal on a world-wide basis.

10 US-4,916,134 teaches novel 4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-azolylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]triazolones having improved antimicrobial properties. Said patent encompasses saperconazole.

US-4,791,111 discloses derivatives of [[4-[4-(4-phenyl-1-piperazinyl)phenoxy]methyl]-1,3-dioxolan-2-yl]methyl]-1H-imidazoles and 1H-1,2,4-triazoles, structurally related to
15 some of the compounds of the present invention, which are taught to have favourable anti-microbial properties.

US-5,039,676 discloses azole-methyl substituted tetrahydrofurans, structurally related to some of the compounds of the present invention, which are taught to have antifungal activity and EP-0,539,938 teaches analogous trisubstituted tetrahydrofuran
20 antifungals.

The present invention concerns novel compounds of formula



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the pharmaceutically acceptable acid or base addition salts thereof and the stereochemically isomeric forms thereof, wherein

A and B taken together form a bivalent radical of formula :

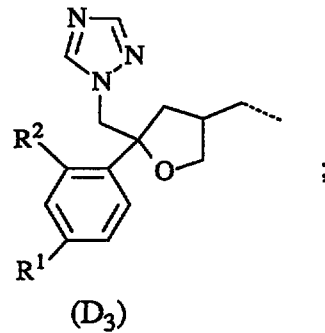
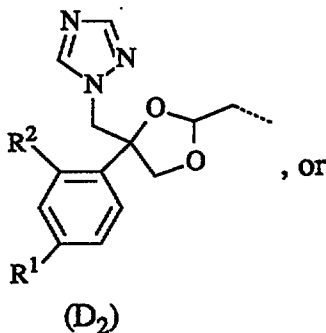
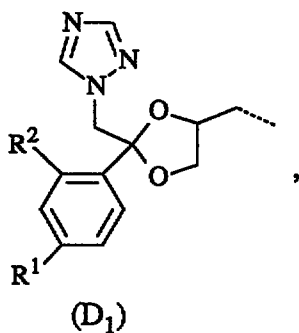
- 30 -N=CH- (a),
 -CH=N- (b),
 -CH₂-CH₂- (c),
 -CH=CH- (d),
 -C(=O)-CH₂- (e),
35 -CH₂-C(=O)- (f),



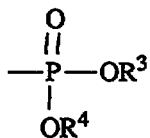
wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula

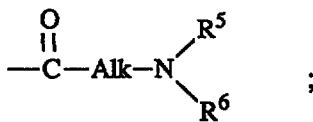
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L is a radical of formula



, or



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Alk is a C₁₋₄alkanediyl radical;

R¹ is halo;

R² is hydrogen or halo;

15 R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or

20 R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said substituted piperazine being a piperazine ring substituted on the 4-position of the piperazine ring with C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.

25 In the definitions hereinabove and hereinafter the term halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl is generic to straight and branch chained hydrocarbons having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and the possible branched isomers thereof; the term "C₁₋₆alkyl" in C₁₋₆alkyloxy,



aminoC₁₋₆alkyl, mono- and di(C₁₋₆alkyl)aminoC₁₋₆alkyl is as defined hereinabove.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic saturated hydrocarbon radicals, in particular the substituents on the dioxolane or tetrahydrofuran ring, may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.



Alk is appropriately methylene or ethanediyl;

R¹ is suitably fluoro, chloro or bromo, preferably fluoro;

R² is suitably hydrogen, fluoro, chloro or bromo, preferably fluoro;

R³ is suitably hydrogen or phenyl, preferably hydrogen;

5 R⁴ is suitably hydrogen or phenyl, preferably hydrogen;

R⁵ is suitably hydrogen, methyl or ethyl;

R⁶ is suitably hydrogen, methyl or ethyl; or

R⁵ and R⁶ are suitably taken together with the nitrogen atom to which they are attached to form a pyrrolidine ring or a substituted piperazine ring.

10 A and B taken together are suitably radicals of formula (a), (b) or (c).

Interesting compounds are those compounds of formula (I) wherein D is a radical of formula (D₁) or (D₂).

15 Particular compounds are those compounds of formula (I) wherein L is a radical formula (L₂) wherein R⁵ and R⁶ each independently are hydrogen or C₁₋₆alkyl; or when taken together with the nitrogen atom to which they are attached form a pyrrolidine, or a piperazine ring substituted with C₁₋₆alkyl or C₁₋₆alkyloxy on the 4-position of the piperazine ring.

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More interesting compounds are those interesting compounds wherein L is a radical of formula (L₁).

25 Preferred compounds of formula (I) are those compounds of formula (I) wherein D is a radical of formula (D₁), wherein R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula (L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.

30 The compounds of formula (I) wherein the substituents on the dioxolane or tetrahydrofuran have the cis-configuration, i.e. wherein the triazolmethylene substituent and the substituted phenoxy methylene substituent are on the same side of the plane of the dioxolane or tetrahydrofuran ring, are preferred.

More preferred compounds are selected from :

35 (±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[2-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl-
5 methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-
1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate(ester) monohydrate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(4-fluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

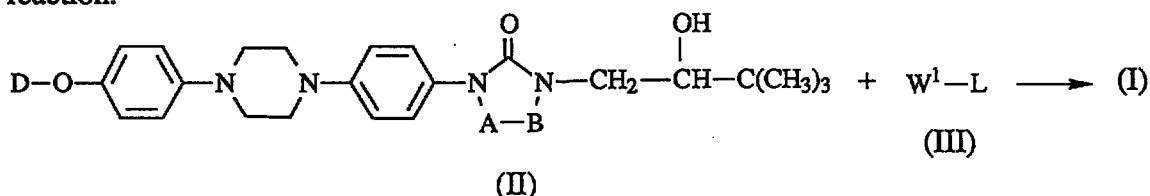
10 (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate monohydrochloride; and

15 (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate.

Most preferred is

(±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-
20 1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-
2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one, the stereochemically
isomeric forms thereof and the base addition salts thereof.

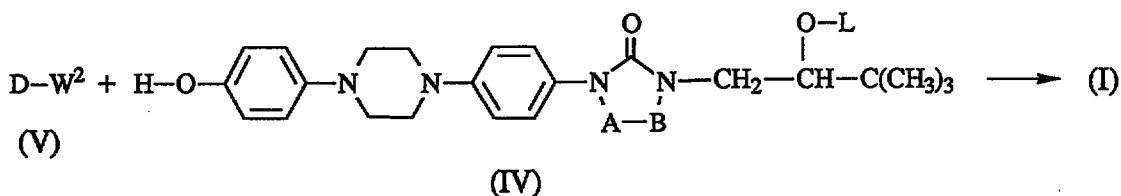
The compounds of formula (I) may generally be prepared by Q-acylation or Q-phosphorylation of an intermediate alcohol of formula (II) with an acylating or phosphorylating reagent of formula (III), wherein W¹ is a reactive leaving group such as, hydroxy or halo. Said reaction may be performed following art-known acylation or phosphorylation procedures, for instance, by stirring the reactants in a reaction-inert solvent, optionally in admixture with a base to pick up the acid that is formed during the reaction.



The compounds of formula (I) may also be prepared by Q-alkylating a phenol of formula (IV) with an alkylating reagent of formula (V), wherein W² is a reactive leaving group such as halo, or a sulfonyloxy group. Said reaction may be performed by stirring the

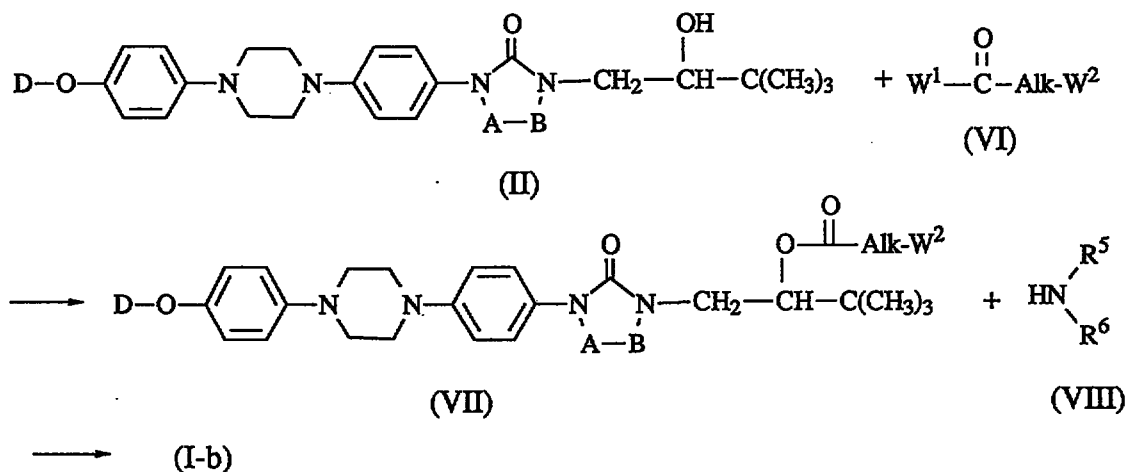


reactants in a reaction-inert solvent, optionally in admixture with a suitable base to pick up the acid that is formed during the reaction. In the compounds and intermediates mentioned hereinafter the substituents are as defined above, unless otherwise indicated.



The preparation of intermediates of formula (V), wherein D is a radical of formula D₁, has been disclosed in U.S. Patent No 4,267,179. The preparation of intermediates of formula (V), wherein D is a radical of formula D₃, has been disclosed in EP-0,539,938.

The compounds of formula (I), wherein L is a radical of formula L₂, said compounds being represented by formula (I-b), may also be prepared by Q-acylating an intermediate of formula (II) with a reagent of formula (VI) and subsequently reacting the thus obtained intermediate of formula (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b).



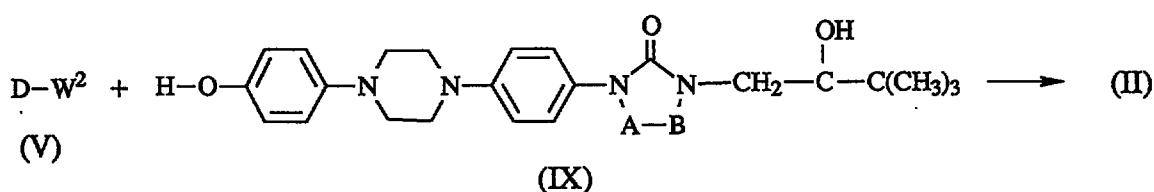
The compounds of formula (I) may also be converted into each other following art-known transformations. For instance, the compounds wherein L is a radical of formula L₁, said compounds being represented by formula (I-a), may be interconverted as follows. Compounds of formula (I-a) wherein R³ and/or R⁴ are C₁₋₆alkyl, phenyl or halophenyl may be transformed into compounds of formula (I-a), wherein R³ and/or R⁴ are hydrogen using art-known hydrolysis procedures, e.g. by reaction with sodium hydroxide in an appropriate solvent, e.g. water or 1,4-dioxane.

The compounds of formula (I-b) may be interconverted into each other as follows.

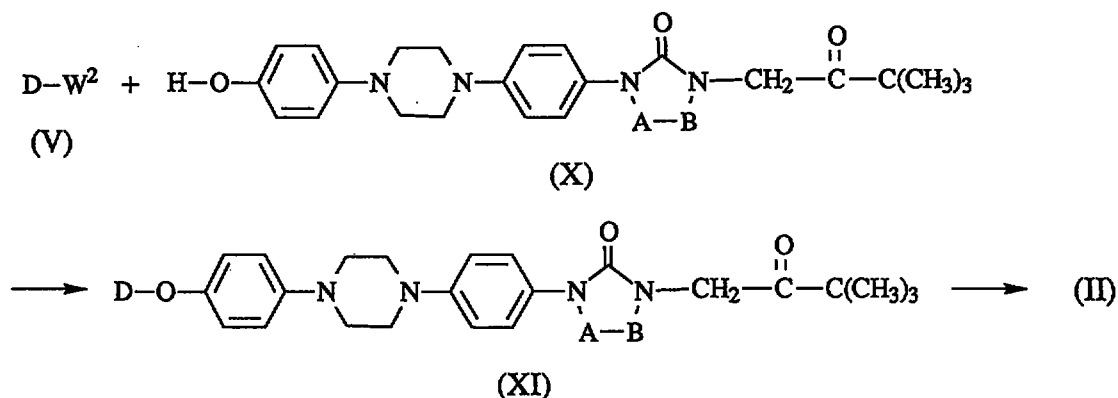


- Compounds of formula (I-b) wherein R^5 and/or R^6 are hydrogen may be transformed into compounds of formula (I-b), wherein R^5 and/or R^6 are C_{1-6} -alkyl, by art-known N-alkylation reactions. Compounds of formula (I-b), wherein R^6 is hydrogen may be converted into compounds of formula (I-b), wherein R^6 is C_{1-6} alkyloxycarbonyl by art-known N-acylation reactions. Conversely compounds of formula (I-b), wherein R^6 is C_{1-6} alkyloxycarbonyl may be converted into compounds of formula (I-b), wherein R^6 is hydrogen by art-known hydrolysis reactions.

- The intermediates of formula (II) may be prepared by Q-alkylating a reagent of formula (IX) with an alkylating reagent of formula (V) following Q-alkylation procedures described hereinabove for the preparation of compounds of formula (I).



- The intermediates of formula (II) may also be prepared by Q-alkylating a reagent of formula (X) with an alkylating reagent of formula (V) following Q-alkylation procedures described hereinabove for the preparation of compounds of formula (I), and subsequently reducing the thus formed intermediate of formula (XI). Said reduction may be performed by stirring the intermediate of formula (XI) with a reducing reagent, such as, for example, sodiumborohydride in a reaction-inert solvent, such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. methanol and mixtures thereof.



The preparation of intermediates of formula (X) is disclosed in US-4,931,444.

$$\text{D-O-C}_6\text{H}_4\text{-N(CH}_2\text{)}_2\text{N-C}_6\text{H}_4\text{-N} \begin{array}{c} \text{O} \\ \parallel \\ \text{A-B} \end{array} \text{C(=O)-N-H} + \text{W}^3\text{-CH}_2\text{-C(=O)-C(CH}_3\text{)}_3 \longrightarrow \text{(XI)}$$


(XII)

Pure stereochemically isomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

The compounds of formula (I), the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof are useful agents for combating fungi and bacteria in vivo. Moreover the compounds of formula (I) are soluble in aqueous solutions, which makes them suitable for intravenous administration. Said compounds are found to be active against a wide variety of fungi, such as *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Fonsecaea* sp., *Microsporium canis*, *Paracoccidioides immitis*, *Trichophyton* sp, *Cladosporium carrionii*, and against bacteria such as, for example, *Erysipelotrix insidiosa*, Staphylococci such as *Staphylococcus haemolyticus* and Streptococci such as *Streptococcus pyogenes*.

The intermediates of formula (II), the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof are also useful in treating or



preventing diseases associated with fungal infections and thus form a further aspect of the present invention. An interesting group of compounds of formula (II) are cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

The present invention also provides compositions for treating or preventing fungal infections comprising an antifungally effective amount of a compound of formula (I) or an intermediate of formula (II) and a pharmaceutically acceptable carrier or diluent.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, e.g. cyclodextrins, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may



be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Appropriate cyclodextrin derivatives are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C₁₋₆alkyl, particularly methyl, ethyl or isopropyl; hydroxyC₁₋₆alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxy-butyl; carboxyC₁₋₆alkyl, particularly carboxymethyl or carboxyethyl; C₁₋₆alkyl-carbonyl, particularly acetyl; C₁₋₆alkyloxycarbonylC₁₋₆alkyl or carboxyC₁₋₆alkyl-oxyC₁₋₆alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C₁₋₆alkylcarbonyloxyC₁₋₆alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

Those of skill in treating warm-blooded animals suffering from diseases caused by fungi and/or bacteria could easily determine the effective amount from the test results given herein. In general, it is contemplated that an effective amount would be from 0.01 mg/kg to 50 mg/kg body weight, and more preferably from 0.05 mg/kg to 20 mg/kg body weight.

Experimental part

Of some compounds of formula (I), the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B".



A. Preparation of the intermediates

Example 1

To a stirred and cooled (ice-bath) mixture of 2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1,2-propanediol (30g), methanesulfonic acid (50ml) and dichloromethane (500ml) was added dropwise 1-bromo-2,2-diethoxyethane (17ml). After stirring for 3 hours at 0°C, the reaction mixture was poured into sodium hydrogen carbonate (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel; CHCl₃/CH₃OH 99:1; CHCl₃/CH₃OH/hexane/CH₃COOC₂H₅ 49:1:20:30). The eluent of the desired fraction was evaporated, yielding 8g (19.0%) of cis-1-[[2-(bromomethyl)-4-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl]-1H-1,2,4-triazole; mp. 76.3°C (interm. 1).

Example 2

A mixture of 2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.01 mol) and sodium hydride (0.012 mol) in N,N-dimethylformamide (100ml) was stirred under nitrogen at 70°C. Intermediate (1) (0.012 mol) was added and the mixture was stirred further overnight. Intermediate (1) (2g) was added again and the mixture was stirred at 70°C for 6 hours and then at room temperature overnight. The mixture was evaporated, the residue was taken up in dichloromethane and washed. The organic layer was dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/hexane/ethyl acetate 50/20/30). The pure fractions were collected and evaporated. The residue was purified further on a glass filter over silica gel/NH₂ (eluent : CH₂Cl₂). The pure fractions were collected and evaporated. The residue was crystallized from ethyl acetate, yielding 2.2g (31%) of (±)-cis-4-[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; 197.1°C (interm. 2).

Example 3

a) A mixture of cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol (0.2mol) in pyridine (400ml) and dichloromethane (250ml) was stirred at room temperature. A solution of 4-cyanobenzoyl chloride (0.22mol) in dichloromethane (150ml) was added dropwise. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from methylbenzene. The crystals were filtered off and dried.



This fraction was purified by column chromatography over a Chiracell OD column (eluent: C₂H₅OH). The first peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.2g (24.9%) of (+)-cis-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl 4-cyanobenzoate; mp. 146.3°C; $[\alpha]_D^{20} = +22.71^\circ$ (c = 0.5% in methanol) (interm. 3). The second peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.4g (25.1%) of (-)-cis-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methyl 4-cyanobenzoate; mp. 144.0°C; $[\alpha]_D^{20} = -22.64^\circ$ (c = 0.5% in methanol) (interm. 4).

b) A mixture of intermediate (3) (0.049mol) and sodium hydroxide 50% (0.059mol) in water (300ml) and 1,4-dioxane (300ml) was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was partitioned between water and dichloromethane. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 10.1g (70%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.0°C; $[\alpha]_D^{20} = +16.58^\circ$ (c = 0.5% in methanol) (interm. 5)

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.2°C; $[\alpha]_D^{20} = -15.97^\circ$ (c = 0.5% in methanol) (interm. 6).

c) A mixture of intermediate (5) (0.02mol) and N,N-diethylethanamine (0.03mol) in dichloromethane (50ml) was stirred at room temperature. Methanesulfonyl chloride (0.03mol) was added dropwise and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated. The residue was partitioned between methylbenzene and water. A precipitate was formed, which was filtered off, dried and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding two fractions. Those fractions were combined and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding 5.88g (78.3%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate(ester); $[\alpha]_D^{20} = +15.50^\circ$ (c = 0.2% in methanol) (interm. 7).

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate (ester); $[\alpha]_D^{20} = -14.50^\circ$ (c = 0.2% in methanol) (interm. 8).

Example 4

a) A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxy-phenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.046mol), 2-(chlorodimethylsilyl)-2-methylpropane (0.063mol) and 1H-imidazole (0.19mol) in *N,N*-dimethylformamide (300ml) was stirred for 4 hours at 50°C. The reaction mixture was poured out into water. The resulting precipitate was filtered off and dried, yielding 21g (83%) of product. A sample (1g) was triturated in 2,2'-oxybispropane, filtered off and dried, yielding 0.7g of (±)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; mp. 196.1°C (interm. 9).

b) Intermediate (9) (0.036mol, mixture of enantiomers) was separated in its enantiomers by column chromatography over a Chiracel® OD column (eluent: *n*-hexanes/2-propanol 65/35). The fraction, corresponding to a first chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 1.56g (7.8%) of (-)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 10). The fraction, corresponding to a second chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 2.28g (11.4%) of (+)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 11).

c) A mixture of intermediate (10) (0.0135mol) in dichloromethane (150ml) was stirred until complete dissolution. A solution of tetrabutylammonium fluoride in tetrahydrofuran (0.015mol) was added in one portion and the reaction mixture was stirred for 1 hour at room temperature. The mixture was diluted with water (150ml) and stirred for 1 hour. The precipitate was filtered off and recrystallized from 2-methoxyethanol. The product was filtered off and dried (vacuum; 60°C), yielding 4.7g (79.6%) of (-)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = -3.14^\circ$ (*c* = 0.1% in *N,N*-dimethylformamide) (interm. 12).

In a similar manner was also prepared :

(+)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = +6.22^\circ$ (*c* = 0.1% in *N,N*-dimethylformamide) (interm. 13).

Example 5

A mixture of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (9.3g), 1-bromo-3,3-dimethyl-2-butanone (2.8g), sodium carbonate (6.4g) and 1,3-dimethyl-2-imidazolidinone (52.2g) was stirred for 5 hours at 100°C. After cooling, the reaction mixture was poured into water. The formed precipitation was filtered off and dissolved in dichloromethane. This solution was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 5.5g (51.3%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.; mp. 176.2°C (interm. 14).

Example 6

To a mixture of intermediate (14) (4.5g), 1,4-dioxane (40ml) and methanol (3ml) was added dropwise a solution of sodium tetrahydroborate (0.3g) in some water. After stirring overnight, the reaction mixture was poured into water and acidified with acetic acid to ± pH 5. The precipitate was filtered off, washed with water, dried and purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanol, yielding 2.2 g (48.7%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 196.4°C (interm. 15).

Example 7

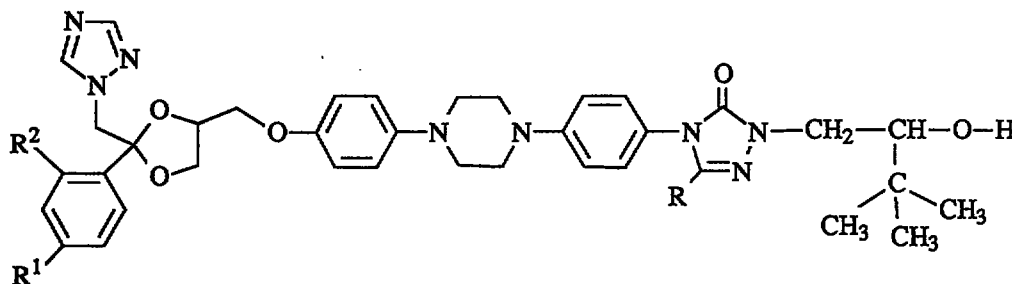
Sodium hydride (0.00675mol) was added portionwise to a mixture of intermediate (12) (0.00595mol) in N,N-dimethylformamide (50ml), stirred at room temperature. The mixture was stirred for 90 minutes at room temperature. Intermediate (7) (0.0054mol) was added and the reaction mixture was stirred for 4 hours at 60°C. The mixture was cooled and the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over an aminopropyl column (eluent: CH₂Cl₂/CH₃OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 50°C), yielding 1.67g (43.1%) of



(+)-[*cis*(+)(B)]-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3*H*-1,2,4-triazol-3-one; mp. 191.9°C; $[\alpha]_D^{20} = +12.03^\circ$ (c = 0.5% in dichloromethane) (interm.20).

5

Table 1



Int. No.	Ex. No.	R	R ¹	R ²	Physical data
15	6	H	F	F	mp. 196.4°C / <i>cis</i>
16	6	H	Cl	Cl	mp. 187.1°C / <i>cis</i>
17	6	H	Cl	H	mp. 201.5°C / <i>cis</i>
18	6	H	F	H	mp. 213.2°C / <i>cis</i>
19	6	H	F	H	mp. 211.1°C / <i>trans</i>
20	7	H	F	F	mp. 191.9°C / $[\alpha]_D^{20} = +12.03^\circ$ (c = 0.5% in dichloromethane) / (+)-[<i>cis</i> (+)(B)]
21	7	H	F	F	mp. 213.2°C / $[\alpha]_D^{20} = -7.89^\circ$ (c = 0.5% in dichloromethane) (-)-[<i>cis</i> (-)(B)]
22	7	H	F	F	mp. 212.5°C / $[\alpha]_D^{20} = +8.38^\circ$ (c = 0.5% in dichloromethane) (+)-[<i>cis</i> (+)(A)]
23	7	H	F	F	mp. 185.6°C / $[\alpha]_D^{20} = -5.08^\circ$ (c = 0.5% in <i>N,N</i> -dimethylformamide) (-)-[<i>cis</i> (-)(A)]

10

Example 8

A mixture of intermediate (2) (0.0025 mol) in dichloromethane (100ml) and methanol



(100ml) was stirred at room temperature. Sodium borohydride (0.005 mol) was added and the mixture was stirred for 4 hours. Water (100ml) was added, the mixture was stirred overnight and separated. The organic layer was washed, dried, filtered off and evaporated. The residue was crystallized from ethyl acetate, yielding 1.6g (89.3%) of
 5 (±)-cis-4-[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 184.1°C (interm. 24).

Example 9

10 A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0035 mol), cis-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanmethanol 4-methylbenzene-sulfonate (the preparation of which is described in European Patent Application 0,539,938) (0.0033 mol) and sodium hydroxide (0.01 mol) in N,N-dimethylformamide
 15 (50ml) was stirred under nitrogen at 50°C for 4 hours and the mixture was stirred further under nitrogen at 60°C for 2 hours. The mixture was cooled and water was added. The product was crystallized out, filtered off and dried. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/ CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was recrystallized from dioxane/2,2'-oxybispropane,
 20 yielding 1.7g (72%) of (±)-cis-4-[4-[4-[4-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 210.8°C (interm. 25).

25 Example 10

Chloroacetyl chloride (0.02 mol) was added to a stirring mixture of intermediate (15) (0.0082 mol) in dichloromethane (100ml). Pyridine (0.037 mol) was added dropwise and the mixture was stirred for 2 hours. Hydrochloric acid 1N (50ml) was added, the mixture was stirred for 2 hours and separated. The organic layer was washed with a
 30 sodium hydrogen carbonate-solution, dried, filtered off and evaporated. The residue was crystallized and triturated in 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 6.3g (96.8%) of product. A sample (1g) was recrystallized from 4-methyl-2-pentanone, yielding 0.6g of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-
 35 1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl chloroacetate (interm. 26).

Example 11

A mixture of (±)-2,4-dihydro-4-(2-hydroxy-3,3-dimethylbutyl)-2-[4-[4-(4-hydroxy-

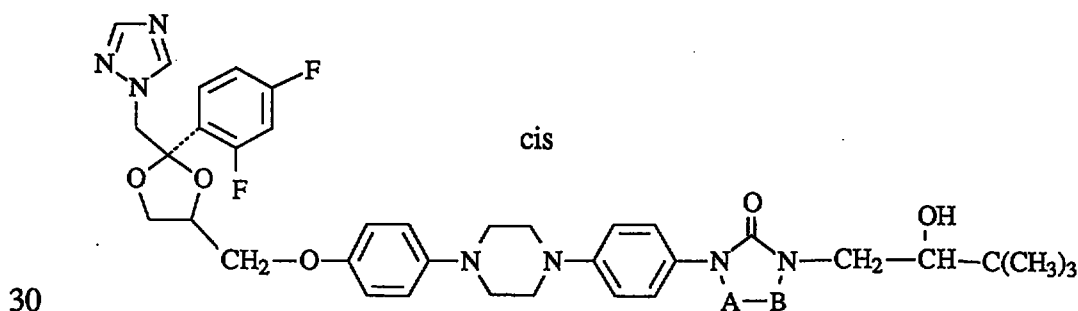


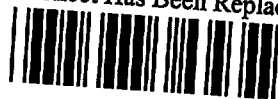
phenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0068 mol), (±)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methane-sulfonate (ester) (0.0082 mol) and sodium hydroxide (0.025 mol) in *N,N*-dimethyl-formamide (100ml) was stirred under nitrogen at 60°C for 4 hours. The mixture was
 5 cooled, water was added and the mixture was stirred. The precipitate was filtered off and dried. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH/ethyl acetate/n-hexane 48/2/30/20). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone, yielding 1.1g (22%) of
 10 (±)-cis-2-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one; mp. 201.2°C (interm. 27).

Example 12

A mixture of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl-
 15 methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(3,3-dimethyl-2-oxobutyl)-1,3-dihydro-2H-imidazol-2-one (0.0036 mol) in methanol (50ml) and dichloromethane (50ml) was stirred. Sodium borohydride (0.01 mol) was added and the mixture was stirred at room temperature for 1 hour. Water (100ml) was added and the mixture was stirred for 1 hour. The mixture was separated and the aqueous layer was
 20 extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was re-crystallized from 4-methyl-2-pentanone, yielding 1.9g (73%) of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-
 25 phenyl]-1-piperazinyl]phenyl]-3-(2-hydroxy-3,3-dimethylbutyl)-2-imidazolidinone; mp. 196.8°C (interm. 29).

Table 2





Interm. No.	Ex. No.	A-B	Physical data
27	11	-N=CH-	mp. 201.2°C
28	11	-(C=O)-C(CH ₃) ₂ -	mp. 141.8°C
29	12	-CH ₂ -CH ₂ -	mp. 196.8°C
30	11	-CH=N	mp. 147.6°C / (+)-[(B-cis), B] / $[\alpha]_D^{20}$ = +1.20° (c = 0.5% in methanol) /

B. Preparation of the final compounds

Example 13

- 5 A mixture of intermediate (15) (0.0014 mol), diphenyl chlorophosphate (0.003 mol) and N,N-dimethyl-4-pyridinamine (1g) in dichloromethane (30ml) was stirred at room temperature for 2 hours. The mixture was purified on a glass filter over silica gel (eluent: CH₂Cl₂ / CH₃OH 98/2). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 1.1g (83%)
- 10 (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate; mp. 170.8°C (comp. 1).

Example 14

- 15 A mixture of compound (1) (0.0029 mol) and a dispersion of sodium hydroxide 50% solution (5g) in 1,4-dioxane (50ml) was stirred at room temperature for 6 hours. Water (200ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid till pH = 2-3. The mixture was extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated.
- 20 The residue was dissolved in a saturated sodium hydrogen carbonate solution (100ml), washed with 2,2'-oxybispropane and extracted twice with dichloromethane (500ml) and methanol (100ml). The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 2-propanol and a little water, yielding 1.2g (46%) of
- 25 (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phenyl sodium phosphate; mp. 167.0°C (comp. 2).

Example 15

- 30 A mixture of compound (1) (0.0038 mol) and sodium hydroxide 50% solution (5g) in



1,4-dioxane (100ml) was stirred at room temperature overnight. Water (600ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid. The precipitate was filtered off (*) and the filtrate was extracted with dichloromethane. The mixture was evaporated. The residue, the precipitate (*) and sodium hydroxide 50% (5g) were stirred at 60°C for 24 hours. Sodium hydroxide 50% (3g) was added again and the mixture was stirred at 60°C for 48 hours. The mixture was cooled, acidified with hydrochloric acid 1N till pH=4 and extracted with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was boiled up in methanol (70ml), filtered off and methanol/ammonia (20ml) was added to the filtrate. The mixture was boiled up in 2-propanol (20ml) and cooled. The mixture was filtered off, the precipitate was dissolved in water (200ml) and washed twice with ethyl acetate. The aqueous layer was acidified with hydrochloric acid 1N and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was dissolved in methanol (70ml) and methanol/ammonia (10ml) was added. The precipitate was filtered off and dried, yielding 1.6g (51%) of (±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate; mp. 189.6°C (comp. 3).

Example 16

Sodium hydroxide 50% (1.4 mol) was added to a suspension of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate (0.07 mol) in 1,4-dioxane (1400 ml) under N₂ flow. The resulting suspension was heated to 60 °C. The reaction solution was stirred for 92 hours at 60 °C. The mixture was allowed to cool to 25 °C. The mixture was poured out into distilled water (5.25 liter) and this mixture was stirred vigorously for 1 hour. The mixture was filtered. The filtrate was acidified (pH = 2.7) with hydrochloric acid and recipitation resulted. The aqueous layer was extracted with CH₂Cl₂ (1 x 2 liter; 1 x 1.5 liter). The combined extracts were dried (Na₂SO₄), filtered and the solvent was evaporated. The residue (71.02 g; 124.7% yield) was stirred in 2-propanol (1050 ml), heated to reflux temperature, stirred and refluxed for 5 min, cooled on an ice bath while stirring vigorously, cooled to 20 °C and stirring was continued overnight. The precipitate was filtered off, washed with 2-propanol (1 x 35 ml), diisopropylether (2 x 35 ml) and dried (vacuum; 50 °C), yielding 48.10 g of (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-



yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate; mp. 156.2°C (comp. 17).

Example 17

5 1-Deoxy-1-(methylamino)-D-glucitol (0.02 mol) was added to a mixture of compound (17) (0.005 mol) in water (70 ml) and the mixture was stirred until complete dissolution (30 min). The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. Ethanol (250 ml) was added and the mixture was stirred vigorously. The mixture was cooled on an ice bath and stirred for 1 hour and precipitation resulted. The
10 mixture was allowed to warm to room temperature (20 °C). The mixture was stirred for 18 hours at room temperature and the resulting precipitate was filtered off, washed with ethanol, with diisopropylether (2 x 10 ml) and dried (vacuum; 50 °C), yielding: 6.14 g (1). The filtrate was evaporated. The residue was dried (vacuum; 50 °C), yielding: 1.98 g (2). Fraction (1) was ground, stirred vigorously for 5 hours in ethanol (200 ml) and
15 the resulting precipitate was filtered off, washed with ethanol (4 x 5 ml) and dried (vacuum; 45-50 °C; 64 hours), yielding: 4.98 g (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one 1-deoxy-1-(methylamine)-D-glucitol (1:2).monohydrate (comp. 18)

Example 18

A mixture of intermediate (26) (0.0025 mol) and pyrrolidine (0.014 mol) in N,N-dimethylformamide (50ml) was stirred at room temperature for 4 hours. Water was added and the mixture was stirred. The precipitate was filtered off, washed with water
25 and purified on a glass filter over silica gel (eluent 1: CH₂Cl₂/CH₃OH 98/2 and eluent 2: CH₂Cl₂/CH₃OH 95/5). The suitable fractions were collected and evaporated. The residue was dissolved in dichloromethane (100ml) and stirred with hydrochloric acid 0.4N (50ml). The mixture was separated and the aqueous layer was extracted four times with dichloromethane. The combined organic layers were dried, filtered off and
30 evaporated. The oily residue was dissolved in dichloromethane, washed with a sodium hydrogen carbonate solution, dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone, yielding 1.1 g (53%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 1-pyrrolidineacetate; mp. 156.7°C (comp. 28).

Example 19

A mixture of intermediate (16) (0.0066 mol), 4-methyl-1-piperazineacetic acid dihydrochloride (0.013 mol), 1,3-dicyclohexylcarbodiimide (0.026 mol) and N,N-



dimethyl-4-pyridinamine (0.026 mol) in dichloromethane (100ml) was stirred at room temperature for 4 hours. Hydrochloric acid 1N (200ml) was added and the mixture was stirred for 1 hour. The precipitate was filtered off, water (600ml) was added and the mixture was separated (*). The aqueous layer was washed with dichloromethane (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 4.5g of fraction 1. (*) The organic layer was washed with hydrochloric acid 1N (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted twice with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 2g of fraction 2. Fractions 1 and 2 were put together and recrystallized from (acetonitrile 2% water)/ 2,2'-oxybispropane, yielding 3.8g (61%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate . monohydrochloride . hemihydrate; mp. 156.0°C (comp. 32).

Example 20

A mixture of compound (17) (0.0034 mol) in a solution of hydrochloric acid in 2-propanol (10ml) and dichloromethane (60ml) was stirred and refluxed for 30 minutes. The mixture was evaporated. The residue was dissolved in water and filtered off. The filtrate was neutralized with a sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (50ml) and washed three times with ethyl acetate (100ml). The aqueous layer was neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from acetonitrile and a little N,N-dimethylformamide, yielding 1.3g (46%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl β-alanine monohydrochloride; mp. 217.9°C (comp. 36).

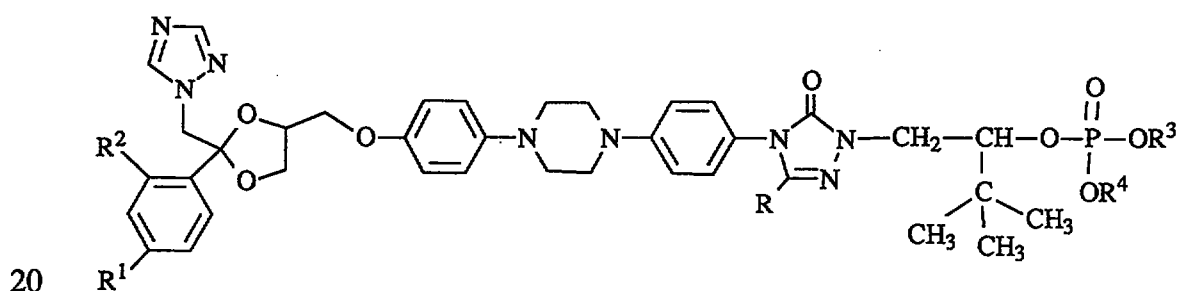
Example 21

A mixture of (±)-cis-N-[1-[3-[1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropoxy]-3-oxopropyl]-1,4-dihydro-4-pyridinylidene]-N-methylmethanaminium chloride monohydrate (0.0024 mol) and pyrrolidine (0.01 mol) in N,N-dimethylformamide (50ml) was stirred at room



- temperature for 1 hour. The mixture was poured into water and extracted three times with dichloromethane. The combined organic layers were washed with water, dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (500ml) and washed three times with ethyl acetate (100ml). The aqueous layer was
- 5 neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (0.5ml). The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH 96/4). The suitable fractions were collected and evaporated. The residue was dissolved in hydrochloric acid 1N (50ml), neutralized with
- 10 pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (5 drops), yielding 1.1g (51%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethyl-
- 15 propyl 1-pyrrolidinepropanoate . monohydrochloride . monohydrate; mp. 154.4°C (comp. 37)

Table 3



Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
1	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 170.8°C
2	14	H	F	F	H	C ₆ H ₅	mp. 167.0°C / Na ⁺
3	15	H	F	F	H	H	mp. 189.6°C / NH ₄ ⁺
4	13	H	Cl	Cl	C ₆ H ₅	C ₆ H ₅	mp. 167.1°C
5	15	H	Cl	Cl	H	H	mp. 188.2°C / NH ₄ ⁺
6	13	H	Cl	H	C ₆ H ₅	C ₆ H ₅	mp. 174.2°C
7	15	H	Cl	H	H	H	mp. 195.5°C / NH ₄ ⁺
8	13	H	F	H	C ₆ H ₅	C ₆ H ₅	mp. 184.6°C
9	15	H	F	H	H	H	mp. 159.8°C / NH ₄ ⁺

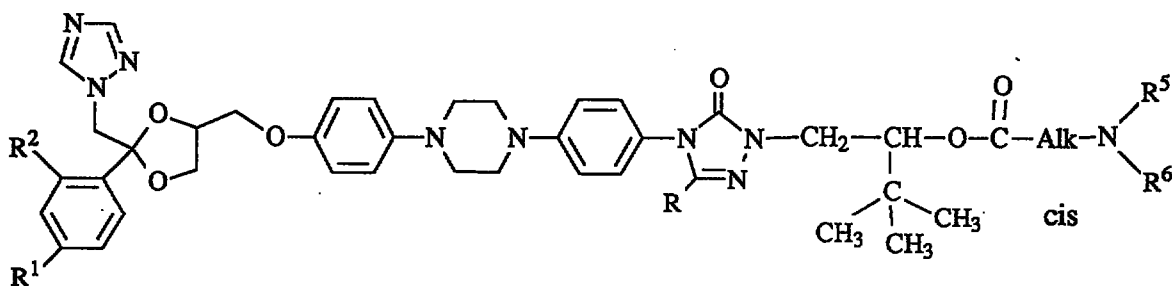


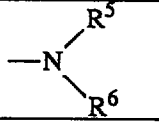
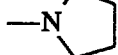
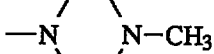
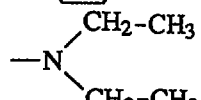
Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
10	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 147.6°C [α] _D ²⁰ = +1.20° (c = 0.5% in methanol) (+)-[(B-cis), B]
11	15	H	F	F	H	H	mp. 200.7°C / NH ₄ ⁺ [α] _D ²⁰ = -15.8° (c = 0.1% in DMF) (+)-[(B-cis), B]
12	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.6°C [α] _D ²⁰ = -15.89° (c = 0.1% in methanol) (-)-[(A-cis), B]
13	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.7°C [α] _D ²⁰ = 13.62° (c = 0.1% in methanol) (-)-[(B-cis), A]
14	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 145.7°C [α] _D ²⁰ = -3.52° (c = 0.1% in methanol) (-)-[(A-cis), A]
15	13	H	F	F	C ₆ H ₅	C ₆ H ₅	cis
16	15	H	F	F	H	H	mp. 201.3°C / NH ₄ ⁺ cis
17	16	H	F	F	H	H	mp. 156.2°C cis 1/2 H ₂ O
18	17	H	F	F	H	H	mp. 117.6°C cis .2 CH ₃ -NH-CH ₂ - (C-OH) ₄ -CH ₂ -OH
19	17	H	F	F	H	H	mp. 184.7°C / cis C(CH ₂ -OH) ₃ NH ₂
20	17	H	F	F	H	H	mp. 251.7°C / .2 Na ⁺ cis. 7/2 H ₂ O



Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
21	15	H	F	F	H	H	mp. 202.7°C / NH ₄ ⁺ / [α] _D ²⁰ = 51.72° (c = 0.5% in DMF) / (-)[(B-cis),A]
22	15	H	F	F	H	H	[(A-cis),A]
23	16	H	F	F	H	H	mp. 171.6°C / [α] _D ²⁰ = +10.93° (c = 0.5% in DMF)
24	16	H	F	F	H	H	[(B-cis),A] · H ₂ O
25	16	H	F	F	H	H	NH ₄ ⁺ / [(A-cis),B]
26	16	H	F	F	H	H	mp. 167.8°C / [α] _D ²⁰ = +12.59° (c = 1% in DMF)
27	15	H	F	F	H	H	[α] _D ²⁰ = 3.70° (c = 0.5% in methanol)

Table 4



Co. No.	Ex. No.	R	R ¹	R ²	Alk		Physical data
28	18	H	F	F	CH ₂		mp. 156.7°C
29	18	H	F	F	CH ₂		mp. 155.3°C
30	18	H	F	F	CH ₂		mp. 166.3°C



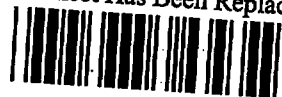
Co. No.	Ex. No.	R	R ¹	R ²	Alk	$\begin{array}{c} \text{R}^5 \\ \\ -\text{N} \\ \\ \text{R}^6 \end{array}$	Physical data
31	18	H	F	F	CH ₂		mp. 171.7°C .2HCl.H ₂ O
32	19	H	Cl	Cl	CH ₂		mp. 156.0°C .2HCl.1/2H ₂ O
33	19	H	F	F	CH ₂ -CH ₂		mp. 213.7°C .HCl
34	19	H	F	F	CH ₂		mp. 201.5°C .HCl
35	19	H	F	F	CH ₂ -CH ₂		-
36	20	H	F	F	CH ₂ -CH ₂		mp. 217.9°C .HCl
37	21	H	F	F	CH ₂ -CH ₂		mp. 154.4°C .HCl.H ₂ O
38	21	H	F	F	CH ₂		mp. 219.5°C .HCl
39	21	H	F	F	CH ₂ -CH ₂		mp. 208.5°C .2HCl

C. Physicochemical exampleExample 225 Solubility

An excess of compound was added to 5 ml of solvent (the type of solvent is specified in the table). The mixture was shaken during 1 hour at room temperature. The precipitate was filtered off. The pH of the remaining solvent was measured and is shown in the table. The concentration of the compound was measured via UV-spectroscopy and is shown in the column "Solubility".

10

Co. No.	Solvent	pH	Solubility (mg/ml)
2	water	7.01	> 6
3	water	6.95	31.93
7	water	6.80	0.35



Co. No.	Solvent	pH	Solubility (mg/ml)
9	water	6.65	2.65
29	0.1 N HCl	1.62	4.89
30	0.1 N HCl	1.65	5.22
33	0.1 N HCl	1.65	> 6
34	0.1 N HCl	1.75	> 6
36	0.1 N HCl	1.25	> 6
37	0.1 N HCl	1.26	> 6
38	0.1 N HCl	1.59	> 6
31	0.1 N HCl	1.53	> 6

D. Pharmacological examples

Example 23

5 Mouse triple mycosis model

The test compounds were evaluated for their activity in a mouse model of fungal infection in which three mycoses - vaginal candidosis, cutaneous trichophytosis and disseminated aspergillosis - were established simultaneously. The mice, in groups of 10, were pretreated with subcutaneous injections of oestradiol valerate (500µg) then inoculated on day 0 with the following : 100 000 colony forming units (CFU)/g of *Aspergillus fumigatus* B19119 intravenously, a suspension containing 10⁸ *Candida albicans* cells intravaginally and a aqueous suspension of *Trichophyton quinckeanum* on lightly scarified dorsal skin. Treatment with the test compounds (orally or intravenously) was begun on the day of infection and continued for 5 days. All animals that died spontaneously and those that survived and were sacrificed on day 6, were sampled for the numbers of *Aspergillus fumigatus* CFU/g in kidney and spleen, for skin lesion scores (0 = no visible lesion; 1 = a few point lesions; 2 = moderate lesions; 3 = severe lesions) and for *Candida albicans* CFU from a vaginal swab.

20 Mouse disseminated *Candida* model

Mice in groups of 10 were infected intravenously with 8 x 10⁵ CFU of *Candida albicans*. Treatment was begun on the day of infection and repeated daily for 9 days. *Candida albicans* CFU/g kidney were measured for all mice that died spontaneously or were killed on day 10.

25

The table indicates the lowest concentrations of the shown compounds that achieved a reduction in mean *Candida* counts of 1 log (i.e. a 10-fold reduction) or more, either in



the triple mycosis model or the disseminated *Candida* infection; also the lowest concentrations that reduced mean skin scores below 1.0 in the cutaneous dermatophytosis component of this model (NT = nor tested, IV = intravenous).

CN	Mouse triple mycosis model				Mouse disseminated <i>Candida</i> model
	Vaginal <i>Candida</i> CFU reduced by 1 log or more		Dermatophyte skin score reduced to ≤ 1		Kidney <i>Candida</i> CFU reduced by 1 log or more
	IV route	oral route	IV route	oral route	IV route
34	2.5	2.5	2.5	2.5	5
3	2.5	2.5	2.5	2.5	10
17	< 2.5	NT	< 2.5	NT	NT

5

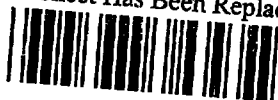
Example 24

Determination of fungal susceptibility.

A panel of *Candida* isolates plus single isolates of the dermatophytes *Microsporum canis*, *Trichophyton rubrum* and *T. mentagrophytes*; *Aspergillus fumigates*, and
 10 *Cryptococcus neoformans* were used to evaluate the activity of the test compounds in vitro. Inocula were prepared as broth cultures (yeasts) or as suspensions of fungal material made from agar slope cultures (moulds). The test compounds were pipetted from DMSO stock solution into water to provide a series of 10-fold dilutions. The fungal inocula were suspended in the growth medium CYG (F.C. Odds, Journal of
 15 Clinical Microbiology, 29, (2735-2740, 1991) at approximately 50000 colony-forming units (CFU) per ml and added to the aqueous test drugs.

The cultures were set up in the 96 wells of plastic microdilution plates and they were incubated for 2 days at 37°C (*Candida* spp.) or for 5 days at 30°C (other fungi). Growth in the microcultures was measured by its optical density (OD) measured at a wavelength
 20 of 405 nm. The OD for cultures with test compounds was calculated as a percentage of the control, drug-free OD. Inhibition of growth to 35% of control or less was recorded as significant inhibition.

Minimal inhibitory concentration (MICs) of intermediates 15, 16, 17, 18, 24 range from
 25 ≤ 0.01 to about 10 μM *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, non-azole-resistant *Candida albicans*, *Candida kefyr*, *Microsporum canis*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, *Aspergillus fumigatus*.

E. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

5 Example 25 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of a sodium hydroxide solution and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were
10 added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I. The resulting solution was filled into suitable containers.

Example 26 : CAPSULES

20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose,
15 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

Example 27 : FILM-COATED TABLETSPreparation of tablet core

20 A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and
25 compressed into tablets, giving 10,000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there
30 were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus
35 obtained mixture in a coating apparatus.

Example 28 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams sodium hydroxide were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was
5 cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Example 29 : SUPPOSITORIES

3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in
10 25 ml polyethylene glycol 400. 12 Grams surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

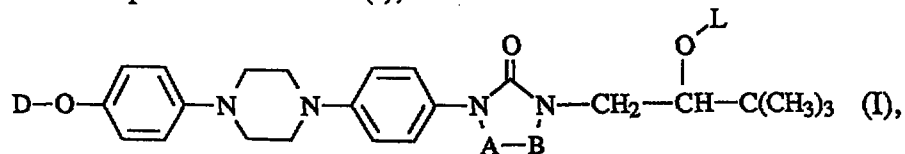


Claims

This Sheet Has Been Replaced



1. A compound of formula (I),



a pharmaceutically acceptable acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein

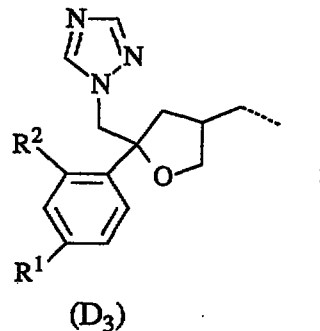
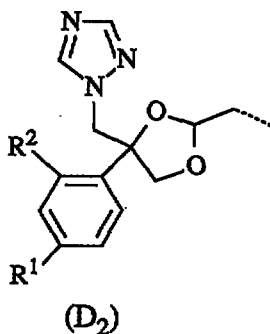
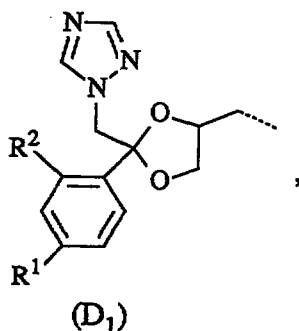
A and B taken together form a bivalent radical of formula :

- 10
- N=CH- (a),
 - CH=N- (b),
 - CH₂-CH₂- (c),
 - CH=CH- (d),
 - C(=O)-CH₂- (e),
 - 15 -CH₂-C(=O)- (f),

wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

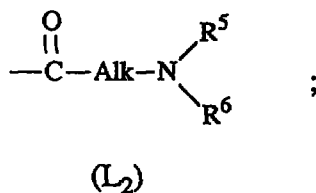
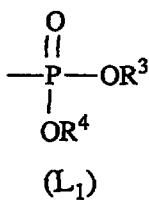
D is a radical of formula

20

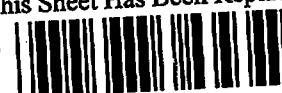


L is a radical of formula

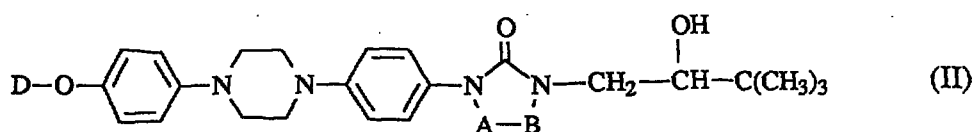
25



Alk is a C₁₋₄alkanediyl radical;



- R¹ is halo;
R² is hydrogen or halo;
R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;
R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;
5 R⁵ is hydrogen or C₁₋₆alkyl;
R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or
R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a
pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said
substituted piperazine being a piperazine ring substituted on the 4-position of the
10 piperazine ring with C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or
di(C₁₋₆alkyl)aminoC₁₋₆alkyl.
2. A compound according to claim 1, wherein D is a radical of formula (D₁) or (D₂).
- 15 3. A compound according to claim 2, wherein D is a radical of formula (D₁), wherein
R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula
(L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.
- 20 4. A compound according to claim 3, wherein the compound is (±)-cis-4-[4-[4-[4-[2-
(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-
phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-
3H-1,2,4-triazol-3-one, a stereochemically isomeric form or a base addition salt form
thereof.
- 25 5. A composition comprising a pharmaceutically acceptable carrier and as active
ingredient an antifungally effective amount of a compound as claimed in any of claims 1
to 4.
- 30 6. A process for preparing a composition as claimed in claim 5 characterized in that a
compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically
acceptable carrier.
- 35 7. A method of inhibiting the development of and/or eliminating fungi in warm-blooded
animals suffering from infections by these fungi, comprising the administration to said
warm-blooded animals of an antifungally effective amount of a compound as claimed in
any of claims 1 to 4.
8. A compound of formula (II)



a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

5 A and B taken together form a bivalent radical of formula :

-N=CH- (a),

-CH=N- (b),

-CH₂-CH₂- (c),

-CH=CH- (d),

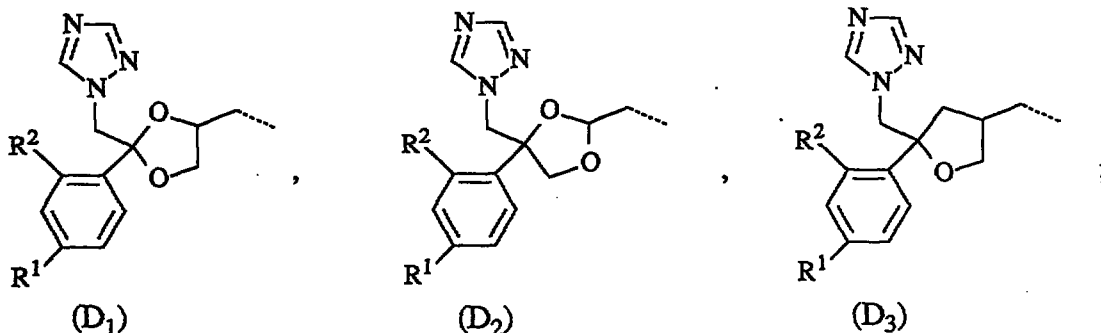
10 -C(=O)-CH₂- (e),

-CH₂-C(=O)- (f),

wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

15

D is a radical of formula



wherein

20 R¹ is halo; and

R² is hydrogen or halo.

9. A compound according to claim 8, wherein the compounds is (±)-cis-4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one, a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof.

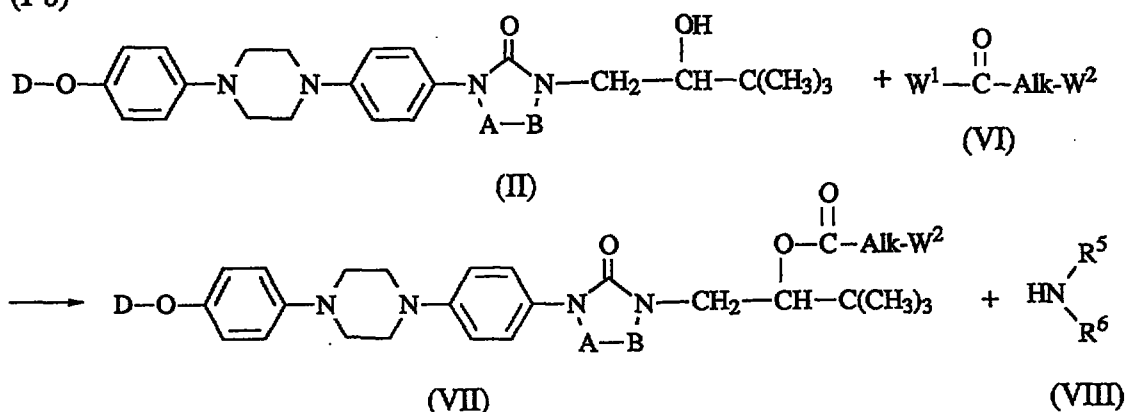
10. A process for preparing a compound as claimed in claim 1 characterized by
30 a) Q-acylating or Q-phosphorylating an intermediate of formula (II) wherein A, B and D are as defined in claim 7 with an acylating or phosphorylating reagent of formula (III),




$$\text{D-O-C}_6\text{H}_4\text{-N(CH}_2\text{)}_2\text{N-C}_6\text{H}_4\text{-N} \begin{array}{c} \text{O} \\ \parallel \\ \text{A-B} \end{array} \text{N-CH}_2\text{-CH(OH)-C(CH}_3\text{)}_3 + \text{W}^1\text{-L} \longrightarrow \text{(I);}$$

(II) (III)

5 b) O-acylating an intermediate of formula (II) with reagent of formula (VI) wherein W¹ is a reactive leaving group such as hydroxy or halo, and W² is a reactive leaving group such as halo or a sulfonyloxy group, and subsequently reacting the thus obtained intermediate (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b)



or converting the compounds of formula (I) into each other following art-known functional group transformation procedures; converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or base; or conversely, converting the salt form into the free base of the free acid by treatment with alkali, respectively an acid; and/or preparing stereochemically isomeric forms thereof.

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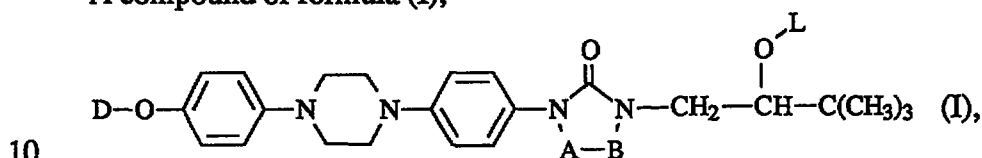


ABSTRACT

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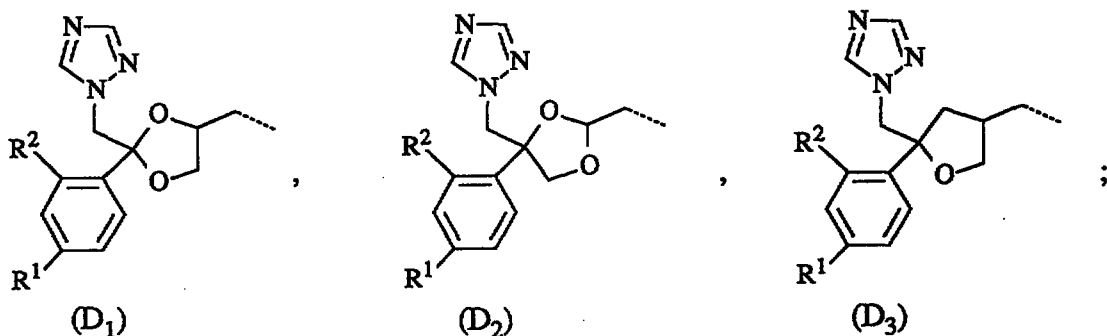
WATERSOLUBLE AZOLE ANTIFUNGALS

A compound of formula (I),

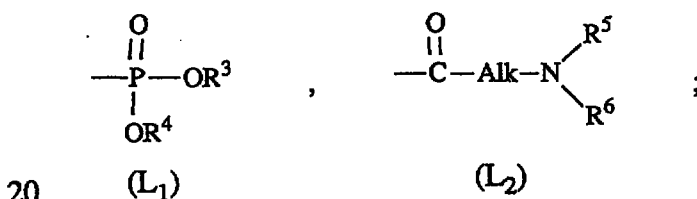


an acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein A and B taken together form -N=CH-, -CH=N-, -CH₂-CH₂, CH=CH-, -C(=O)-CH₂-, -CH₂-C(=O); D is a radical of formula

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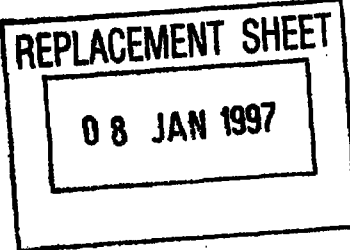
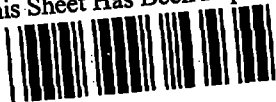
L is a radical of formula



Alk is a C₁₋₄alkanediyl radical; R¹ is halo; R² is hydrogen or halo; R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁵ is hydrogen or C₁₋₆alkyl; R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a heterocyclic ring. Active intermediates, compositions and methods of preparing compounds, compositions are described.

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2-07280022



WATERSOLUBLE AZOLE ANTIFUNGALS

The present invention is concerned with novel water-soluble broad-spectrum azole antifungals as well as the antifungally active precursors thereof.

Systemic fungal infections in man are relatively rare in temperate countries and many of the fungi that can become pathogenic normally live commensally in the body or are common in the environment. However, the past few decades have witnessed an increasing incidence of numerous life-threatening systemic fungal infections world-wide and these now represent a major threat to many susceptible patients, particularly those already hospitalized. Most of the increase can be attributed to improved survival of immunocompromised patients and the chronic use of antimicrobial agents. Moreover, the flora typical of many common fungal infections is also changing and this is presenting an epidemiological challenge of increasing importance. Patients at greatest risk include those with impaired immune functioning, either directly as a result of immunosuppression from cytotoxic drugs or HIV infection, or secondary to other debilitating diseases such as cancer, acute leukaemia, invasive surgical techniques or prolonged exposure to anti-microbial agents. The most common systemic fungal infections in man are candidosis, aspergillosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and cryptococcosis.

Antifungals such as ketoconazole, itraconazole and fluconazole are being increasingly employed for the treatment and prophylaxis of systemic fungal infections in immunocompromised patients. However, concern about fungal resistance to some of these agents, especially the more narrow spectrum ones, e.g. fluconazole, is growing. Worse still, it is recognized in the medical world that about 40% of the people suffering from severe systemic fungal infections are hardly able, or not at all to receive medication via oral administration. This inability is due to the fact that such patients are in coma or suffer from severe gastroparesis. Hence the use of insoluble or sparingly soluble antifungals such as itraconazole or saperconazole, that are difficult to administer intravenously, is heavily impeded.

Consequently, there is a need for new antifungals, preferably broad-spectrum antifungals, against which there is no existing resistance and which can be administered



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intravenously. Preferably the antifungal should also be available in a pharmaceutical composition suitable for oral administration. This enables the physician to continue treatment with the same drug after the patient has recovered from his condition which required intravenous administration of said drug.

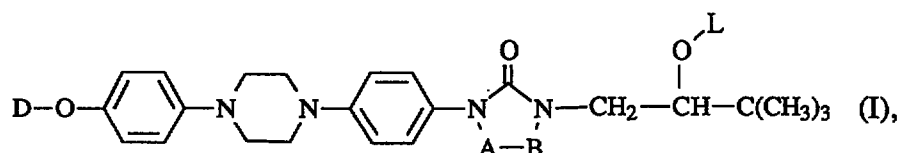
US-4,267,179 discloses heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxymethyl-1,3-dioxolan-2-yl)-methyl-1H-imidazoles and 1H-1,2,4-triazoles useful as antifungal and antibacterial agents. Said patent encompasses itraconazole, which is now available as a broadspectrum antifungal on a world-wide basis.

US-4,916,134 teaches novel 4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-azolylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]triazolones having improved antimicrobial properties. Said patent encompasses saperconazole.

US-4,791,111 discloses derivatives of [[4-[4-(4-phenyl-1-piperazinyl)phenoxy]methyl]-1,3-dioxolan-2-yl]methyl]-1H-imidazoles and 1H-1,2,4-triazoles, structurally related to some of the compounds of the present invention, which are taught to have favourable anti-microbial properties.

US-5,039,676 discloses azole-methyl substituted tetrahydrofurans, structurally related to some of the compounds of the present invention, which are taught to have antifungal activity and EP-0,539,938 teaches analogous trisubstituted tetrahydrofuran antifungals.

The present invention concerns novel compounds of formula



the pharmaceutically acceptable acid or base addition salts thereof and the stereochemically isomeric forms thereof, wherein

A and B taken together form a bivalent radical of formula :

- N=CH- (a),
- CH=N- (b),
- CH₂-CH₂- (c),
- CH=CH- (d),
- C(=O)-CH₂- (e),
- CH₂-C(=O)- (f),

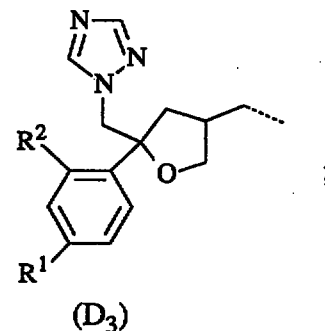
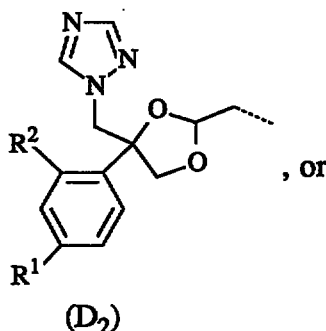
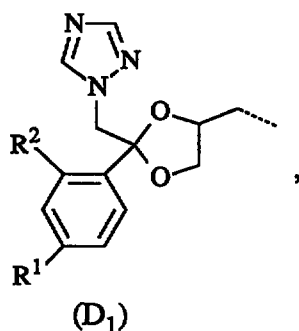


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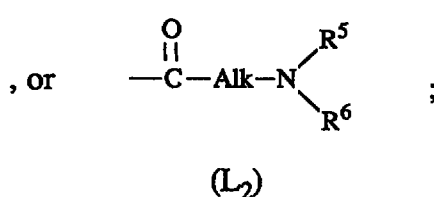
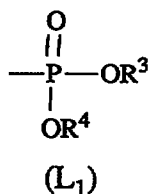
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wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical;

R¹ is halo;

R² is hydrogen or halo;

R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or

R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said substituted piperazine being a piperazine ring substituted on the 4-position of the piperazine ring with C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.

In the definitions hereinabove and hereinafter the term halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl is generic to straight and branch chained hydrocarbons having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and the possible branched isomers thereof; the term "C₁₋₆alkyl" in C₁₋₆alkyloxy,



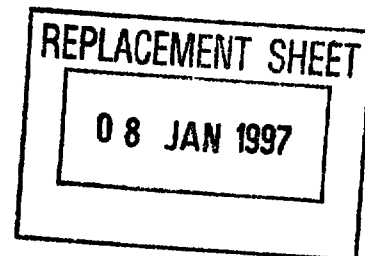
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aminoC₁₋₆alkyl, mono- and di(C₁₋₆alkyl)aminoC₁₋₆alkyl is as defined hereinabove.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic saturated hydrocarbon radicals, in particular the substituents on the dioxolane or tetrahydrofuran ring, may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.



Alk is appropriately methylene or ethanediyl;

R¹ is suitably fluoro, chloro or bromo, preferably fluoro;

R² is suitably hydrogen, fluoro, chloro or bromo, preferably fluoro;

R³ is suitably hydrogen or phenyl, preferably hydrogen;

R⁴ is suitably hydrogen or phenyl, preferably hydrogen;

R⁵ is suitably hydrogen, methyl or ethyl;

R⁶ is suitably hydrogen, methyl or ethyl; or

R⁵ and R⁶ are suitably taken together with the nitrogen atom to which they are attached to form a pyrrolidine ring or a substituted piperazine ring.

A and B taken together are suitably radicals of formula (a), (b) or (c).

Interesting compounds are those compounds of formula (I) wherein D is a radical of formula (D₁) or (D₂).

Particular compounds are those compounds of formula (I) wherein L is a radical formula (L₂) wherein R⁵ and R⁶ each independently are hydrogen or C₁₋₆alkyl; or when taken together with the nitrogen atom to which they are attached form a pyrrolidine, or a piperazine ring substituted with C₁₋₆alkyl or C₁₋₆alkyloxy on the 4-position of the piperazine ring.

More interesting compounds are those interesting compounds wherein L is a radical of formula (L₁).

Preferred compounds of formula (I) are those compounds of formula (I) wherein D is a radical of formula (D₁), wherein R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula (L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.

The compounds of formula (I) wherein the substituents on the dioxolane or tetrahydrofuran have the cis-configuration, i.e. wherein the triazolmethylene substituent and the substituted phenoxy methylene substituent are on the same side of the plane of the dioxolane or tetrahydrofuran ring, are preferred.

More preferred compounds are selected from :

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;



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(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate(ester) monohydrate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(4-fluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

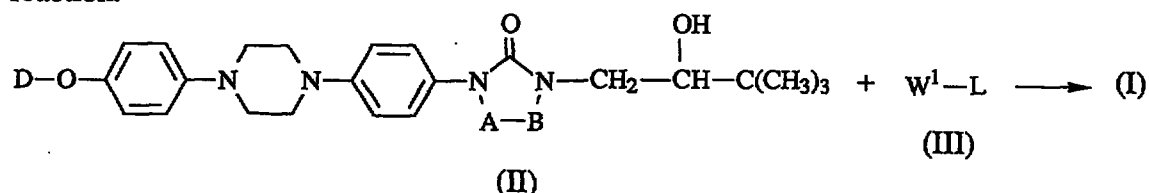
(±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate monohydrochloride; and

(±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonoxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate.

Most preferred is

(±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonoxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one, the stereochemically isomeric forms thereof and the base addition salts thereof.

The compounds of formula (I) may generally be prepared by Q-acylation or Q-phosphorylation of an intermediate alcohol of formula (II) with an acylating or phosphorylating reagent of formula (III), wherein W^1 is a reactive leaving group such as, hydroxy or halo. Said reaction may be performed following art-known acylation or phosphorylation procedures, for instance, by stirring the reactants in a reaction-inert solvent, optionally in admixture with a base to pick up the acid that is formed during the reaction.

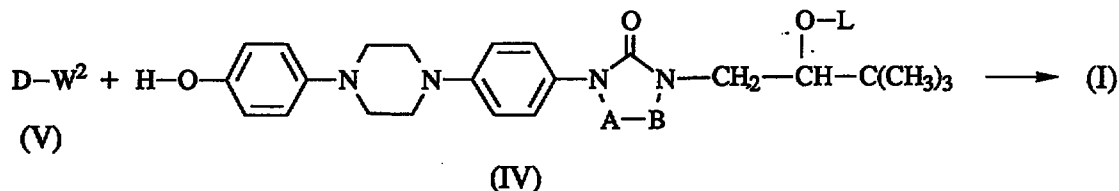


The compounds of formula (I) may also be prepared by Q-alkylating a phenol of formula (IV) with an alkylating reagent of formula (V), wherein W^2 is a reactive leaving group such as halo, or a sulfonyloxy group. Said reaction may be performed by stirring the



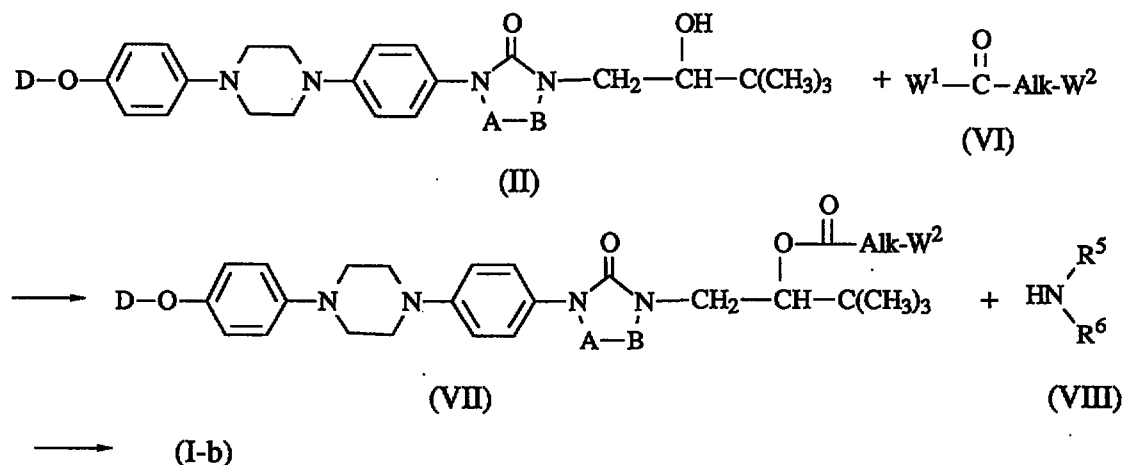
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reactants in a reaction-inert solvent, optionally in admixture with a suitable base to pick up the acid that is formed during the reaction. In the compounds and intermediates mentioned hereinafter the substituents are as defined above, unless otherwise indicated.



The preparation of intermediates of formula (V), wherein D is a radical of formula D₁, has been disclosed in U.S. Patent No 4,267,179. The preparation of intermediates of formula (V), wherein D is a radical of formula D₃, has been disclosed in EP-0,539,938.

The compounds of formula (I), wherein L is a radical of formula L₂, said compounds being represented by formula (I-b), may also be prepared by Q-acylating an intermediate of formula (II) with a reagent of formula (VI) and subsequently reacting the thus obtained intermediate of formula (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b).

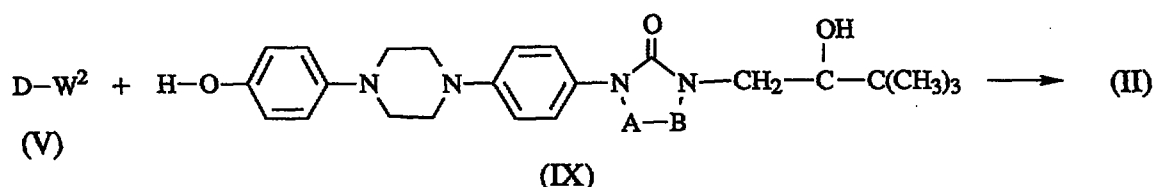


The compounds of formula (I) may also be converted into each other following art-known transformations. For instance, the compounds wherein L is a radical of formula L₁, said compounds being represented by formula (I-a), may be interconverted as follows. Compounds of formula (I-a) wherein R³ and/or R⁴ are C₁₋₆alkyl, phenyl or halophenyl may be transformed into compounds of formula (I-a), wherein R³ and/or R⁴ are hydrogen using art-known hydrolysis procedures, e.g. by reaction with sodium hydroxide in an appropriate solvent, e.g. water or 1,4-dioxane.

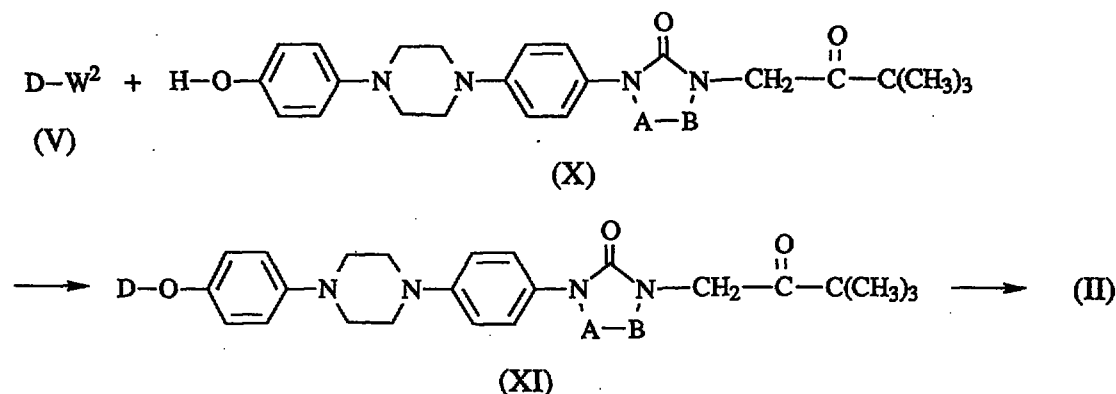
The compounds of formula (I-b) may be interconverted into each other as follows.

Compounds of formula (I-b) wherein R⁵ and/or R⁶ are hydrogen may be transformed into compounds of formula (I-b), wherein R⁵ and/or R⁶ are C₁₋₆-alkyl, by art-known N-alkylation reactions. Compounds of formula (I-b), wherein R⁶ is hydrogen may be converted into compounds of formula (I-b), wherein R⁶ is C₁₋₆-alkyloxycarbonyl by art-known N-acylation reactions. Conversely compounds of formula (I-b), wherein R⁶ is C₁₋₆-alkyloxycarbonyl may be converted into compounds of formula (I-b), wherein R⁶ is hydrogen by art-known hydrolysis reactions.

The intermediates of formula (II) may be prepared by Q-alkylating a reagent of formula (IX) with an alkylating reagent of formula (V) following Q-alkylation procedures described hereinabove for the preparation of compounds of formula (I).



The intermediates of formula (II) may also be prepared by Q-alkylating a reagent of formula (X) with an alkylating reagent of formula (V) following Q-alkylation procedures described hereinabove for the preparation of compounds of formula (I), and subsequently reducing the thus formed intermediate of formula (XI). Said reduction may be performed by stirring the intermediate of formula (XI) with a reducing reagent, such as, for example, sodiumborohydride in a reaction-inert solvent, such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. methanol and mixtures thereof.

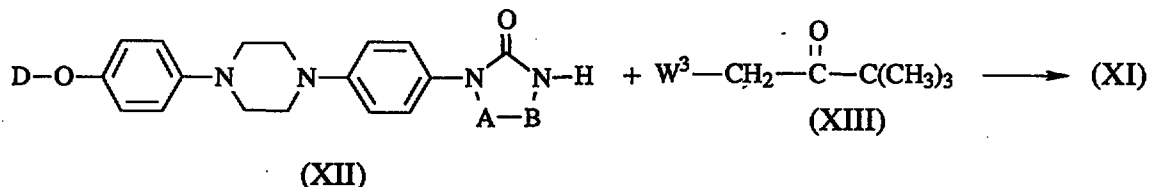


The preparation of intermediates of formula (X) is disclosed in US-4,931,444.



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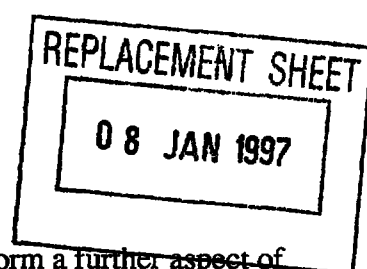
The intermediates of formula (XI) may also be prepared by N-alkylating an intermediate of formula (XII) following art-known N-alkylation procedures with an alkylating reagent of formula (XIII), wherein W^3 is an appropriate leaving group, e.g. halo.



Pure stereochemically isomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

The compounds of formula (I), the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof are useful agents for combating fungi and bacteria in vivo. Moreover the compounds of formula (I) are soluble in aqueous solutions, which makes them suitable for intravenous administration. Said compounds are found to be active against a wide variety of fungi, such as *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Fonsecaea* sp., *Microsporium canis*, *Paracoccidioides immitis*, *Trichophyton* sp, *Cladosporium carrionii*, and against bacteria such as, for example, *Erysipelotrix insidiosa*, Staphylococci such as *Staphylococcus haemolyticus* and Streptococci such as *Streptococcus pyogenes*.

The intermediates of formula (II), the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof are also useful in treating or

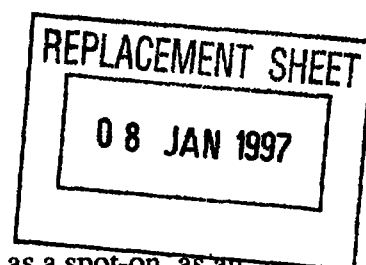


preventing diseases associated with fungal infections and thus form a further aspect of the present invention. An interesting group of compounds of formula (II) are cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

The present invention also provides compositions for treating or preventing fungal infections comprising an antifungally effective amount of a compound of formula (I) or an intermediate of formula (II) and a pharmaceutically acceptable carrier or diluent.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, e.g. cyclodextrins, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may



be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Appropriate cyclodextrin derivatives are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxy-butyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkyl-carbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy C_{1-6} alkyl-oxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

Those of skill in treating warm-blooded animals suffering from diseases caused by fungi and/or bacteria could easily determine the effective amount from the test results given herein. In general, it is contemplated that an effective amount would be from 0.01 mg/kg to 50 mg/kg body weight, and more preferably from 0.05 mg/kg to 20 mg/kg body weight.

Experimental part

Of some compounds of formula (I), the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B".



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A. Preparation of the intermediatesExample 1

To a stirred and cooled (ice-bath) mixture of 2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1,2-propanediol (30g), methanesulfonic acid (50ml) and dichloromethane (500ml) was added dropwise 1-bromo-2,2-diethoxyethane (17ml). After stirring for 3 hours at 0°C, the reaction mixture was poured into sodium hydrogen carbonate (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel; CHCl₃/CH₃OH 99:1; CHCl₃/CH₃OH/hexane/CH₃COOC₂H₅ 49:1:20:30). The eluent of the desired fraction was evaporated, yielding 8g (19.0%) of cis-1-[[2-(bromomethyl)-4-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl]-1H-1,2,4-triazole; mp. 76.3°C (interm. 1).

Example 2

A mixture of 2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.01 mol) and sodium hydride (0.012 mol) in N,N-dimethylformamide (100ml) was stirred under nitrogen at 70°C. Intermediate (1) (0.012 mol) was added and the mixture was stirred further overnight. Intermediate (1) (2g) was added again and the mixture was stirred at 70°C for 6 hours and then at room temperature overnight. The mixture was evaporated, the residue was taken up in dichloromethane and washed. The organic layer was dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/hexane/ethyl acetate 50/20/30). The pure fractions were collected and evaporated. The residue was purified further on a glass filter over silica gel/NH₂ (eluent : CH₂Cl₂). The pure fractions were collected and evaporated. The residue was crystallized from ethyl acetate, yielding 2.2g (31%) of (±)-cis-4-[4-[4-[4-[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; 197.1°C (interm. 2).

Example 3

a) A mixture of cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol (0.2mol) in pyridine (400ml) and dichloromethane (250ml) was stirred at room temperature. A solution of 4-cyanobenzoyl chloride (0.22mol) in dichloromethane (150ml) was added dropwise. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from methylbenzene. The crystals were filtered off and dried.



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This fraction was purified by column chromatography over a Chiracell OD column (eluent: C₂H₅OH). The first peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.2g (24.9%) of (+)-cis-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl 4-cyanobenzoate; mp. 146.3°C; $[\alpha]_D^{20} = +22.71^\circ$ (c = 0.5% in methanol) (interm. 3). The second peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.4g (25.1%) (-)-cis-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methyl 4-cyanobenzoate; mp. 144.0°C; $[\alpha]_D^{20} = -22.64^\circ$ (c = 0.5% in methanol) (interm. 4).

b) A mixture of intermediate (3) (0.049mol) and sodium hydroxide 50% (0.059mol) in water (300ml) and 1,4-dioxane (300ml) was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was partitioned between water and dichloromethane. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 10.1g (70%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.0°C; $[\alpha]_D^{20} = +16.58^\circ$ (c = 0.5% in methanol) (interm. 5)

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.2°C; $[\alpha]_D^{20} = -15.97^\circ$ (c = 0.5% in methanol) (interm. 6).

c) A mixture of intermediate (5) (0.02mol) and N,N-diethylethanamine (0.03mol) in dichloromethane (50ml) was stirred at room temperature. Methanesulfonyl chloride (0.03mol) was added dropwise and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated. The residue was partitioned between methylbenzene and water. A precipitate was formed, which was filtered off, dried and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding two fractions. Those fractions were combined and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding 5.88g (78.3%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate(ester); $[\alpha]_D^{20} = +15.50^\circ$ (c = 0.2% in methanol) (interm. 7).

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate (ester); $[\alpha]_D^{20} = -14.50^\circ$ (c = 0.2% in methanol) (interm. 8).



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Example 4

- a) A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.046mol), 2-(chlorodimethylsilyl)-2-methylpropane (0.063mol) and 1H-imidazole (0.19mol) in N,N-dimethylformamide (300ml) was stirred for 4 hours at 50°C. The reaction mixture was poured out into water. The resulting precipitate was filtered off and dried, yielding 21g (83%) of product. A sample (1g) was triturated in 2,2'-oxybispropane, filtered off and dried, yielding 0.7g of (±)-4-[4-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; mp. 196.1°C (interm. 9).
- b) Intermediate (9) (0.036mol, mixture of enantiomers) was separated in its enantiomers by column chromatography over a Chiracell® OD column (eluent: n-hexanes/2-propanol 65/35). The fraction, corresponding to a first chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 1.56g (7.8%) of (-)-4-[4-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 10). The fraction, corresponding to a second chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 2.28g (11.4%) of (+)-4-[4-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 11).
- c) A mixture of intermediate (10) (0.0135mol) in dichloromethane (150ml) was stirred until complete dissolution. A solution of tetrabutylammonium fluoride in tetrahydrofuran (0.015mol) was added in one portion and the reaction mixture was stirred for 1 hour at room temperature. The mixture was diluted with water (150ml) and stirred for 1 hour. The precipitate was filtered off and recrystallized from 2-methoxyethanol. The product was filtered off and dried (vacuum; 60°C), yielding 4.7g (79.6%) of (-)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = -3.14^\circ$ (c = 0.1% in N,N-dimethylformamide) (interm. 12).

In a similar manner was also prepared :

- (+)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = +6.22^\circ$ (c = 0.1% in N,N-dimethylformamide) (interm. 13).



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Example 5

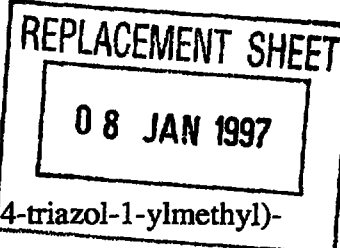
A mixture of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (9.3g), 1-bromo-3,3-dimethyl-2-butanone (2.8g), sodium carbonate (6.4g) and 1,3-dimethyl-2-imidazolidinone (52.2g) was stirred for 5 hours at 100°C. After cooling, the reaction mixture was poured into water. The formed precipitation was filtered off and dissolved in dichloromethane. This solution was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 5.5g (51.3%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.; mp. 176.2°C (interm. 14).

Example 6

To a mixture of intermediate (14) (4.5g), 1,4-dioxane (40ml) and methanol (3ml) was added dropwise a solution of sodium tetrahydroborate (0.3g) in some water. After stirring overnight, the reaction mixture was poured into water and acidified with acetic acid to $\pm$ pH 5. The precipitate was filtered off, washed with water, dried and purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanol, yielding 2.2 g (48.7%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 196.4°C (interm. 15).

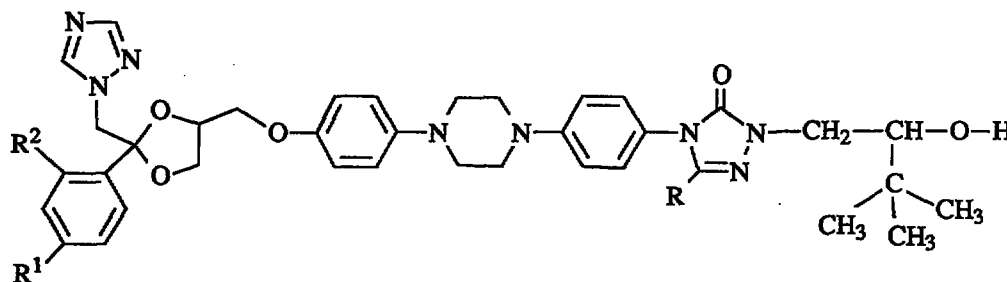
Example 7

Sodium hydride (0.00675mol) was added portionwise to a mixture of intermediate (12) (0.00595mol) in N,N-dimethylformamide (50ml), stirred at room temperature. The mixture was stirred for 90 minutes at room temperature. Intermediate (7) (0.0054mol) was added and the reaction mixture was stirred for 4 hours at 60°C. The mixture was cooled and the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over an aminopropyl column (eluent: CH₂Cl₂/CH₃OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 50°C), yielding 1.67g (43.1%) of



(+)-[cis](+)(B)]-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 191.9°C; $[\alpha]_D^{20} = +12.03^\circ$ (c = 0.5% in dichloromethane) (interm.20).

Table 1



Int. No.	Ex. No.	R	R ¹	R ²	Physical data
15	6	H	F	F	mp. 196.4°C / cis
16	6	H	Cl	Cl	mp. 187.1°C / cis
17	6	H	Cl	H	mp. 201.5°C / cis
18	6	H	F	H	mp. 213.2°C / cis
19	6	H	F	H	mp. 211.1°C / trans
20	7	H	F	F	mp. 191.9°C / $[\alpha]_D^{20} = + 12.03^\circ$ (c = 0.5% in dichloromethane) / (+)-[cis(+)(B)]
21	7	H	F	F	mp. 213.2°C / $[\alpha]_D^{20} = - 7.89^\circ$ (c = 0.5% in dichloromethane) (-)-[cis(-)(B)]
22	7	H	F	F	mp. 212.5°C / $[\alpha]_D^{20} = + 8.38^\circ$ (c = 0.5% in dichloromethane) (+)-[cis(+)(A)]
23	7	H	F	F	mp. 185.6°C / $[\alpha]_D^{20} = - 5.08^\circ$ (c = 0.5% in N,N-dimethylformamide) (-)-[cis(-)(A)]

10

Example 8

A mixture of intermediate (2) (0.0025 mol) in dichloromethane (100ml) and methanol



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(100ml) was stirred at room temperature. Sodium borohydride (0.005 mol) was added and the mixture was stirred for 4 hours. Water (100ml) was added, the mixture was stirred overnight and separated. The organic layer was washed, dried, filtered off and evaporated. The residue was crystallized from ethyl acetate, yielding 1.6g (89.3%) of (±)-cis-4-[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 184.1°C (interm. 24).

Example 9

A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0035 mol), cis-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanmethanol 4-methylbenzene-sulfonate (the preparation of which is described in European Patent Application 0,539,938) (0.0033 mol) and sodium hydroxide (0.01 mol) in *N,N*-dimethylformamide (50ml) was stirred under nitrogen at 50°C for 4 hours and the mixture was stirred further under nitrogen at 60°C for 2 hours. The mixture was cooled and water was added. The product was crystallized out, filtered off and dried. The residue was purified on a glass filter over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was recrystallized from dioxane/2,2'-oxybispropane, yielding 1.7g (72%) of (±)-cis-4-[4-[4-[4-[[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 210.8°C (interm. 25).

Example 10

Chloroacetyl chloride (0.02 mol) was added to a stirring mixture of intermediate (15) (0.0082 mol) in dichloromethane (100ml). Pyridine (0.037 mol) was added dropwise and the mixture was stirred for 2 hours. Hydrochloric acid 1N (50ml) was added, the mixture was stirred for 2 hours and separated. The organic layer was washed with a sodium hydrogen carbonate-solution, dried, filtered off and evaporated. The residue was crystallized and triturated in 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 6.3g (96.8%) of product. A sample (1g) was recrystallized from 4-methyl-2-pentanone, yielding 0.6g of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl chloroacetate (interm. 26).

Example 11

A mixture of (±)-2,4-dihydro-4-(2-hydroxy-3,3-dimethylbutyl)-2-[4-[4-(4-hydroxy-



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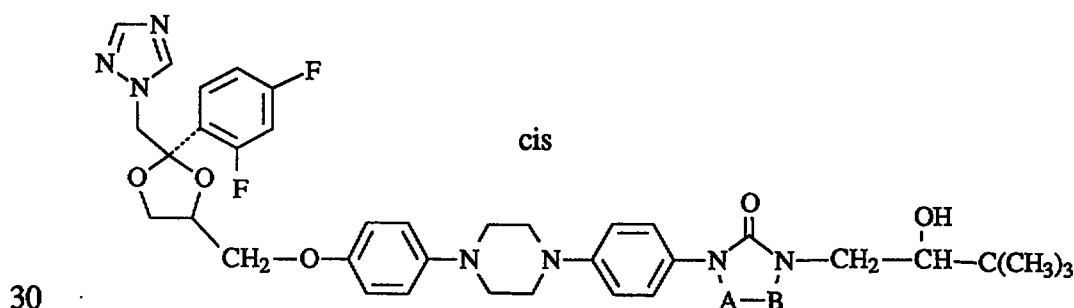
-18-

phenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0068 mol), (±)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methane-sulfonate (ester) (0.0082 mol) and sodium hydroxide (0.025 mol) in *N,N*-dimethylformamide (100ml) was stirred under nitrogen at 60°C for 4 hours. The mixture was cooled, water was added and the mixture was stirred. The precipitate was filtered off and dried. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH/ethyl acetate/n-hexane 48/2/30/20). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone, yielding 1.1g (22%) of (±)-cis-2-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one; mp. 201.2°C (interm. 27).

Example 12

A mixture of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(3,3-dimethyl-2-oxobutyl)-1,3-dihydro-2H-imidazol-2-one (0.0036 mol) in methanol (50ml) and dichloromethane (50ml) was stirred. Sodium borohydride (0.01 mol) was added and the mixture was stirred at room temperature for 1 hour. Water (100ml) was added and the mixture was stirred for 1 hour. The mixture was separated and the aqueous layer was extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone, yielding 1.9g (73%) of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(2-hydroxy-3,3-dimethylbutyl)-2-imidazolidinone; mp. 196.8°C (interm. 29).

Table 2





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Interm. No.	Ex. No.	A-B	Physical data
27	11	-N=CH-	mp. 201.2°C
28	11	-(C=O)-C(CH ₃) ₂ -	mp. 141.8°C
29	12	-CH ₂ -CH ₂ -	mp. 196.8°C
30	11	-CH=N	mp. 147.6°C / (+)-[(B-cis), B] / $[\alpha]_D^{20}$ = +1.20° (c = 0.5% in methanol) /

B. Preparation of the final compounds

Example 13

A mixture of intermediate (15) (0.0014 mol), diphenyl chlorophosphate (0.003 mol) and *N,N*-dimethyl-4-pyridinamine (1g) in dichloromethane (30ml) was stirred at room temperature for 2 hours. The mixture was purified on a glass filter over silica gel (eluent: CH₂Cl₂ / CH₃OH 98/2). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 1.1g (83%) (±)-*cis*-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate; mp. 170.8°C (comp. 1).

Example 14

A mixture of compound (1) (0.0029 mol) and a dispersion of sodium hydroxide 50% solution (5g) in 1,4-dioxane (50ml) was stirred at room temperature for 6 hours. Water (200ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid till pH = 2-3. The mixture was extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was dissolved in a saturated sodium hydrogen carbonate solution (100ml), washed with 2,2'-oxybispropane and extracted twice with dichloromethane (500ml) and methanol (100ml). The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 2-propanol and a little water, yielding 1.2g (46%) of (±)-*cis*-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phenyl sodium phosphate; mp. 167.0°C (comp. 2).

Example 15

A mixture of compound (1) (0.0038 mol) and sodium hydroxide 50% solution (5g) in



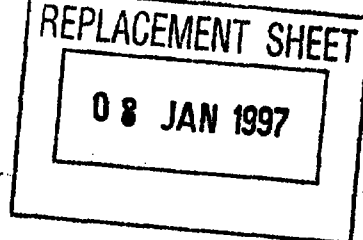
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-20-

1,4-dioxane (100ml) was stirred at room temperature overnight. Water (600ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid. The precipitate was filtered off (*) and the filtrate was extracted with dichloromethane. The mixture was evaporated. The residue, the precipitate (*) and sodium hydroxide 50% (5g) were stirred at 60°C for 24 hours. Sodium hydroxide 50% (3g) was added again and the mixture was stirred at 60°C for 48 hours. The mixture was cooled, acidified with hydrochloric acid 1N till pH=4 and extracted with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was boiled up in methanol (70ml), filtered off and methanol/ammonia (20ml) was added to the filtrate. The mixture was boiled up in 2-propanol (20ml) and cooled. The mixture was filtered off, the precipitate was dissolved in water (200ml) and washed twice with ethyl acetate. The aqueous layer was acidified with hydrochloric acid 1N and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was dissolved in methanol (70ml) and methanol/ammonia (10ml) was added. The precipitate was filtered off and dried, yielding 1.6g (51%) of (±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate; mp. 189.6°C (comp. 3).

Example 16

Sodium hydroxide 50% (1.4 mol) was added to a suspension of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate (0.07 mol) in 1,4-dioxane (1400 ml) under N₂ flow. The resulting suspension was heated to 60 °C. The reaction solution was stirred for 92 hours at 60 °C. The mixture was allowed to cool to 25 °C. The mixture was poured out into distilled water (5.25 liter) and this mixture was stirred vigorously for 1 hour. The mixture was filtered. The filtrate was acidified (pH = 2.7) with hydrochloric acid and recipitation resulted. The aqueous layer was extracted with CH₂Cl₂ (1 x 2 liter; 1 x 1.5 liter). The combined extracts were dried (Na₂SO₄), filtered and the solvent was evaporated. The residue (71.02 g; 124.7% yield) was stirred in 2-propanol (1050 ml), heated to reflux temperature, stirred and refluxed for 5 min, cooled on an ice bath while stirring vigorously, cooled to 20 °C and stirring was continued overnight. The precipitate was filtered off, washed with 2-propanol (1 x 35 ml), diisopropylether (2 x 35 ml) and dried (vacuum; 50 °C), yielding 48.10 g of (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-



yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate; mp. 156.2°C (comp. 17).

Example 17

1-Deoxy-1-(methylamino)-D-glucitol (0.02 mol) was added to a mixture of compound (17) (0.005 mol) in water (70 ml) and the mixture was stirred until complete dissolution (30 min). The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. Ethanol (250 ml) was added and the mixture was stirred vigorously. The mixture was cooled on an ice bath and stirred for 1 hour and precipitation resulted. The mixture was allowed to warm to room temperature (20 °C). The mixture was stirred for 18 hours at room temperature and the resulting precipitate was filtered off, washed with ethanol, with diisopropylether (2 x 10 ml) and dried (vacuum; 50 °C), yielding: 6.14 g (1). The filtrate was evaporated. The residue was dried (vacuum; 50 °C), yielding: 1.98 g (2). Fraction (1) was ground, stirred vigorously for 5 hours in ethanol (200 ml) and the resulting precipitate was filtered off, washed with ethanol (4 x 5 ml) and dried (vacuum; 45-50 °C; 64 hours), yielding: 4.98 g (±)-cis-4-[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one 1-deoxy-1-(methylamine)-D-glucitol (1:2).monohydrate (comp. 18)

Example 18

A mixture of intermediate (26) (0.0025 mol) and pyrrolidine (0.014 mol) in *N,N*-dimethylformamide (50ml) was stirred at room temperature for 4 hours. Water was added and the mixture was stirred. The precipitate was filtered off, washed with water and purified on a glass filter over silica gel (eluent 1: CH₂Cl₂/CH₃OH 98/2 and eluent 2: CH₂Cl₂/CH₃OH 95/5). The suitable fractions were collected and evaporated. The residue was dissolved in dichloromethane (100ml) and stirred with hydrochloric acid 0.4N (50ml). The mixture was separated and the aqueous layer was extracted four times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The oily residue was dissolved in dichloromethane, washed with a sodium hydrogen carbonate solution, dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone, yielding 1.1 g (53%) of (±)-cis-1-[[4-[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 1-pyrrolidineacetate; mp. 156.7°C (comp. 28).

Example 19

A mixture of intermediate (16) (0.0066 mol), 4-methyl-1-piperazineacetic acid dihydrochloride (0.013 mol), 1,3-dicyclohexylcarbodiimide (0.026 mol) and *N,N*-



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dimethyl-4-pyridinamine (0.026 mol) in dichloromethane (100ml) was stirred at room temperature for 4 hours. Hydrochloric acid 1N (200ml) was added and the mixture was stirred for 1 hour. The precipitate was filtered off, water (600ml) was added and the mixture was separated (*). The aqueous layer was washed with dichloromethane (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 4.5g of fraction 1. (*) The organic layer was washed with hydrochloric acid 1N (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted twice with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 2g of fraction 2. Fractions 1 and 2 were put together and recrystallized from (acetonitrile 2% water)/ 2,2'-oxybispropane, yielding 3.8g (61%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate . monohydrochloride . hemihydrate; mp. 156.0°C (comp. 32).

Example 20

A mixture of compound (17) (0.0034 mol) in a solution of hydrochloric acid in 2-propanol (10ml) and dichloromethane (60ml) was stirred and refluxed for 30 minutes. The mixture was evaporated. The residue was dissolved in water and filtered off. The filtrate was neutralized with a sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (50ml) and washed three times with ethyl acetate (100ml). The aqueous layer was neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from acetonitrile and a little N,N-dimethylformamide, yielding 1.3g (46%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl β-alanine monohydrochloride; mp. 217.9°C (comp. 36).

Example 21

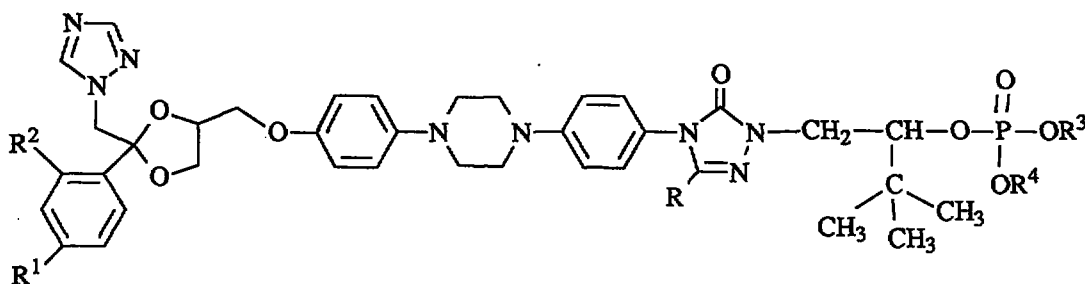
A mixture of (±)-cis-N-[1-[3-[1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropoxy]-3-oxopropyl]-1,4-dihydro-4-pyridinylidene]-N-methylmethanaminium chloride monohydrate (0.0024 mol) and pyrrolidine (0.01 mol) in N,N-dimethylformamide (50ml) was stirred at room



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temperature for 1 hour. The mixture was poured into water and extracted three times with dichloromethane. The combined organic layers were washed with water, dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (500ml) and washed three times with ethyl acetate (100ml). The aqueous layer was neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (0.5ml). The residue was purified on a glass filter over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 96/4). The suitable fractions were collected and evaporated. The residue was dissolved in hydrochloric acid 1N (50ml), neutralized with pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (5 drops), yielding 1.1g (51%) of ($\pm$)-cis-1-[[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethyl-propyl 1-pyrrolidinepropanoate . monohydrochloride . monohydrate; mp. 154.4°C (comp. 37)

Table 3



Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
1	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 170.8°C
2	14	H	F	F	H	C ₆ H ₅	mp. 167.0°C / Na ⁺
3	15	H	F	F	H	H	mp. 189.6°C / NH ₄ ⁺
4	13	H	Cl	Cl	C ₆ H ₅	C ₆ H ₅	mp. 167.1°C
5	15	H	Cl	Cl	H	H	mp. 188.2°C / NH ₄ ⁺
6	13	H	Cl	H	C ₆ H ₅	C ₆ H ₅	mp. 174.2°C
7	15	H	Cl	H	H	H	mp. 195.5°C / NH ₄ ⁺
8	13	H	F	H	C ₆ H ₅	C ₆ H ₅	mp. 184.6°C
9	15	H	F	H	H	H	mp. 159.8°C / NH ₄ ⁺



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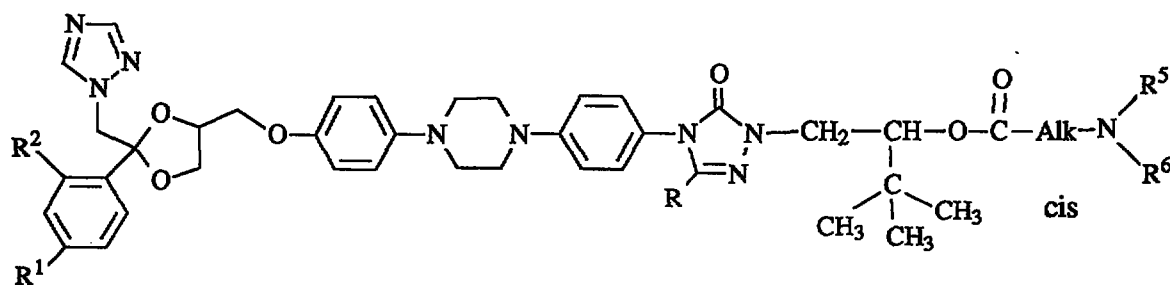
Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
10	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 147.6°C [α] _D ²⁰ = +1.20° (c = 0.5% in methanol) (+)-[(B-cis), B]
11	15	H	F	F	H	H	mp. 200.7°C / NH ₄ ⁺ [α] _D ²⁰ = -15.8° (c = 0.1% in DMF) (+)-[(B-cis), B]
12	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.6°C [α] _D ²⁰ = -15.89° (c = 0.1% in methanol) (-)-[(A-cis), B]
13	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.7°C [α] _D ²⁰ = 13.62° (c = 0.1% in methanol) (-)-[(B-cis), A]
14	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 145.7°C [α] _D ²⁰ = -3.52° (c = 0.1% in methanol) (-)-[(A-cis), A]
15	13	H	F	F	C ₆ H ₅	C ₆ H ₅	cis
16	15	H	F	F	H	H	mp. 201.3°C / NH ₄ ⁺ cis
17	16	H	F	F	H	H	mp. 156.2°C cis 1/2 H ₂ O
18	17	H	F	F	H	H	mp. 117.6°C cis .2 CH ₃ -NH-CH ₂ -(C-OH) ₄ -CH ₂ -OH
19	17	H	F	F	H	H	mp. 184.7°C / cis C(CH ₂ -OH) ₃ NH ₂
20	17	H	F	F	H	H	mp. 251.7°C / .2 Na ⁺ cis. 7/2 H ₂ O

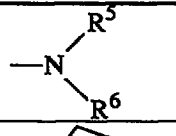
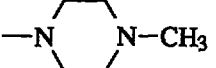
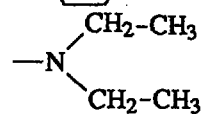


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Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
21	15	H	F	F	H	H	mp. 202.7°C / NH ₄ ⁺ / [α] _D ²⁰ = 51.72° (c = 0.5% in DMF) / (-)[(B-cis),A]
22	15	H	F	F	H	H	[(A-cis),A]
23	16	H	F	F	H	H	mp. 171.6°C / [α] _D ²⁰ = +10.93° (c = 0.5% in DMF)
24	16	H	F	F	H	H	[(B-cis),A] · H ₂ O
25	16	H	F	F	H	H	NH ₄ ⁺ / [(A-cis),B]
26	16	H	F	F	H	H	mp. 167.8°C / [α] _D ²⁰ = +12.59° (c = 1% in DMF)
27	15	H	F	F	H	H	[α] _D ²⁰ = 3.70° (c = 0.5% in methanol)

Table 4



Co. No.	Ex. No.	R	R ¹	R ²	Alk		Physical data
28	18	H	F	F	CH ₂		mp. 156.7°C
29	18	H	F	F	CH ₂		mp. 155.3°C
30	18	H	F	F	CH ₂		mp. 166.3°C



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Co. No.	Ex. No.	R	R ¹	R ²	Alk	$\begin{array}{c} \text{R}^5 \\ \\ -\text{N} \\ \\ \text{R}^6 \end{array}$	Physical data
31	18	H	F	F	CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N}-(\text{CH}_2)_2-\text{OH}$	mp. 171.7°C .2HCl.H ₂ O
32	19	H	Cl	Cl	CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N}-\text{CH}_3$	mp. 156.0°C .2HCl.1/2H ₂ O
33	19	H	F	F	CH ₂ -CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N}-\text{CH}_3$	mp. 213.7°C .HCl
34	19	H	F	F	CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N}-\text{CH}_3$	mp. 201.5°C .HCl
35	19	H	F	F	CH ₂ -CH ₂	$-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-\text{CH}_3$	-
36	20	H	F	F	CH ₂ -CH ₂	NH ₂	mp. 217.9°C .HCl
37	21	H	F	F	CH ₂ -CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}$	mp. 154.4°C .HCl.H ₂ O
38	21	H	F	F	CH ₂	NH ₂	mp. 219.5°C .HCl
39	21	H	F	F	CH ₂ -CH ₂	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N}-(\text{CH}_2)_2-\text{OH}$	mp. 208.5°C .2HCl

C. Physicochemical exampleExample 22Solubility

An excess of compound was added to 5 ml of solvent (the type of solvent is specified in the table). The mixture was shaken during 1 hour at room temperature. The precipitate was filtered off. The pH of the remaining solvent was measured and is shown in the table. The concentration of the compound was measured via UV-spectroscopy and is shown in the column "Solubility".

Co. No.	Solvent	pH	Solubility (mg/ml)
2	water	7.01	> 6
3	water	6.95	31.93
7	water	6.80	0.35



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Co. No.	Solvent	pH	Solubility (mg/ml)
9	water	6.65	2.65
29	0.1 N HCl	1.62	4.89
30	0.1 N HCl	1.65	5.22
33	0.1 N HCl	1.65	> 6
34	0.1 N HCl	1.75	> 6
36	0.1 N HCl	1.25	> 6
37	0.1 N HCl	1.26	> 6
38	0.1 N HCl	1.59	> 6
31	0.1 N HCl	1.53	> 6

D. Pharmacological examples

Example 23

Mouse triple mycosis model

The test compounds were evaluated for their activity in a mouse model of fungal infection in which three mycoses - vaginal candidosis, cutaneous trichophytosis and disseminated aspergillosis - were established simultaneously. The mice, in groups of 10, were pretreated with subcutaneous injections of oestradiol valerate (500µg) then inoculated on day 0 with the following : 100 000 colony forming units (CFU)/g of *Aspergillus fumigatus* B19119 intravenously, a suspension containing 10^8 *Candida albicans* cells intravaginally and a aqueous suspension of *Trichophyton quinckeanum* on lightly scarified dorsal skin. Treatment with the test compounds (orally or intravenously) was begun on the day of infection and continued for 5 days. All animals that died spontaneously and those that survived and were sacrificed on day 6, were sampled for the numbers of *Aspergillus fumigatus* CFU/g in kidney and spleen, for skin lesion scores (0 = no visible lesion; 1 = a few point lesions; 2 = moderate lesions; 3 = severe lesions) and for *Candida albicans* CFU from a vaginal swab.

Mouse disseminated *Candida* model

Mice in groups of 10 were infected intravenously with 8×10^5 CFU of *Candida albicans*. Treatment was begun on the day of infection and repeated daily for 9 days. *Candida albicans* CFU/g kidney were measured for all mice that died spontaneously or were killed on day 10.

The table indicates the lowest concentrations of the shown compounds that achieved a reduction in mean *Candida* counts of 1 log (i.e. a 10-fold reduction) or more, either in



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the triple mycosis model or the disseminated *Candida* infection; also the lowest concentrations that reduced mean skin scores below 1.0 in the cutaneous dermatophytosis component of this model (NT = not tested, IV = intravenous).

CN	Mouse triple mycosis model				Mouse disseminated <i>Candida</i> model
	Vaginal <i>Candida</i> CFU reduced by 1 log or more		Dermatophyte skin score reduced to ≤ 1		Kidney <i>Candida</i> CFU reduced by 1 log or more
	IV route	oral route	IV route	oral route	IV route
34	2.5	2.5	2.5	2.5	5
3	2.5	2.5	2.5	2.5	10
17	< 2.5	NT	< 2.5	NT	NT

Example 24

Determination of fungal susceptibility.

A panel of *Candida* isolates plus single isolates of the dermatophytes *Microsporum canis*, *Trichophyton rubrum* and *T. mentagrophytes*; *Aspergillus fumigatus*, and *Cryptococcus neoformans* were used to evaluate the activity of the test compounds in vitro. Inocula were prepared as broth cultures (yeasts) or as suspensions of fungal material made from agar slope cultures (moulds). The test compounds were pipetted from DMSO stock solution into water to provide a series of 10-fold dilutions. The fungal inocula were suspended in the growth medium CYG (F.C. Odds, Journal of Clinical Microbiology, 29, (2735-2740, 1991) at approximately 50000 colony-forming units (CFU) per ml and added to the aqueous test drugs.

The cultures were set up in the 96 wells of plastic microdilution plates and they were incubated for 2 days at 37°C (*Candida* spp.) or for 5 days at 30°C (other fungi). Growth in the microcultures was measured by its optical density (OD) measured at a wavelength of 405 nm. The OD for cultures with test compounds was calculated as a percentage of the control, drug-free OD. Inhibition of growth to 35% of control or less was recorded as significant inhibition.

Minimal inhibitory concentration (MICs) of intermediates 15, 16, 17, 18, 24 range from ≤ 0.01 to about 10 μM *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, non-azole-resistant *Candida albicans*, *Candida kefyr*, *Microsporum canis*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, *Aspergillus fumigatus*.



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E. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 25 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of a sodium hydroxide solution and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I.. The resulting solution was filled into suitable containers.

Example 26 : CAPSULES

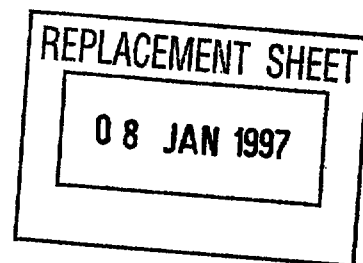
20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

Example 27 : FILM-COATED TABLETSPreparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10,000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

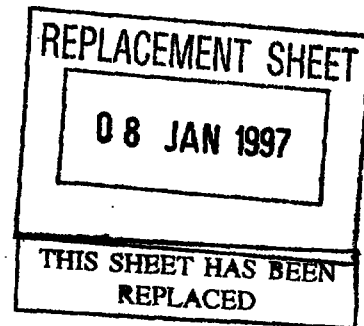


Example 28 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams sodium hydroxide were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

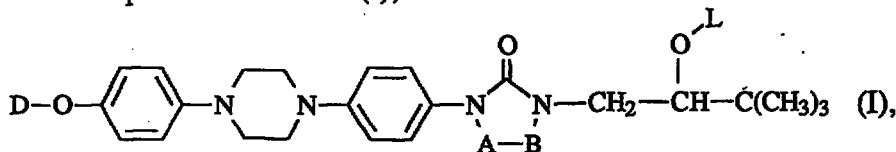
Example 29 : SUPPOSITORIES

3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

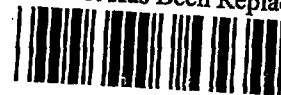


Claims

1. A compound of formula (I),



This Sheet Has Been Replaced



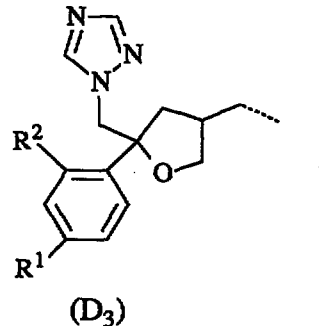
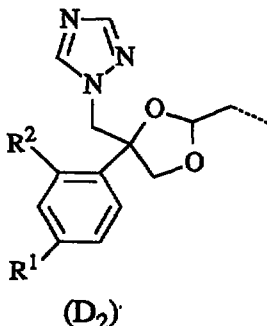
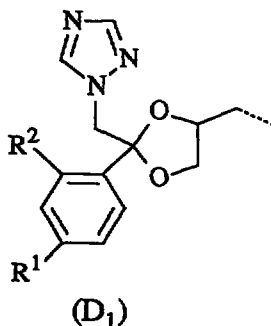
a pharmaceutically acceptable acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein

A and B taken together form a bivalent radical of formula :

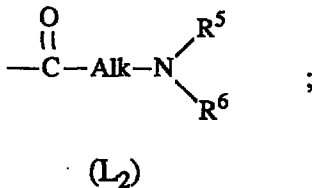
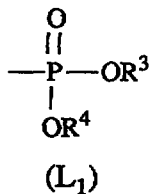
- N=CH- (a),
- CH=N- (b),
- CH₂-CH₂- (c),
- CH=CH- (d),
- C(=O)-CH₂- (e),
- CH₂-C(=O)- (f),

wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical;



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R¹ is halo;

R² is hydrogen or halo;

R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

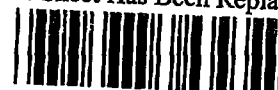
R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or

R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said substituted piperazine being a piperazine ring substituted on the 4-position of the piperazine ring with C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.

2. A compound according to claim 1, wherein D is a radical of formula (D₁) or (D₂).
3. A compound according to claim 2, wherein D is a radical of formula (D₁), wherein R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula (L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.
4. A compound according to claim 3, wherein the compound is (±)-cis-4-[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one, a stereochemically isomeric form or a base addition salt form thereof.
5. A composition comprising a pharmaceutically acceptable carrier and as active ingredient an antifungally effective amount of a compound as claimed in any of claims 1 to 4.
6. A process for preparing a composition as claimed in claim 5 characterized in that a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
7. A method of inhibiting the development of and/or eliminating fungi in warm-blooded animals suffering from infections by these fungi, comprising the administration to said warm-blooded animals of an antifungally effective amount of a compound as claimed in any of claims 1 to 4.
8. A compound of formula (II)

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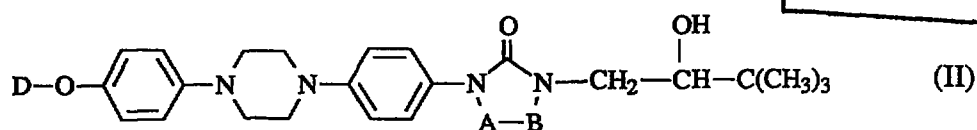


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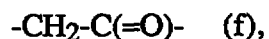
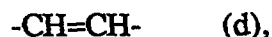
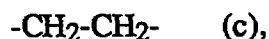
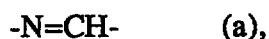
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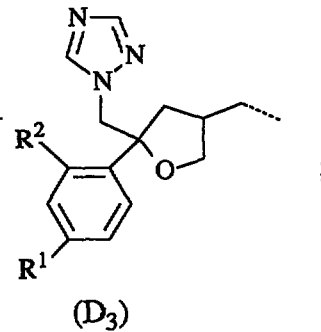
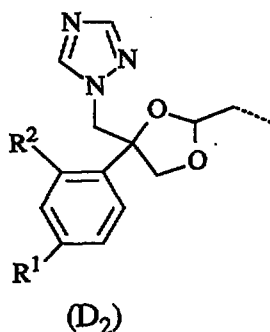
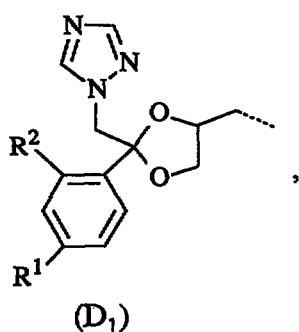
a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

A and B taken together form a bivalent radical of formula :



wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula



wherein

R¹ is halo; and

R² is hydrogen or halo.

9. A compound according to claim 8, wherein the compound is (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one, a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof.

10. A process for preparing a compound as claimed in claim 1 characterized by

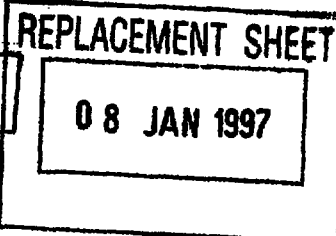
a) O-acylating or O-phosphorylating an intermediate of formula (II) wherein A, B and D are as defined in claim 7 with an acylating or phosphorylating reagent of formula (III),

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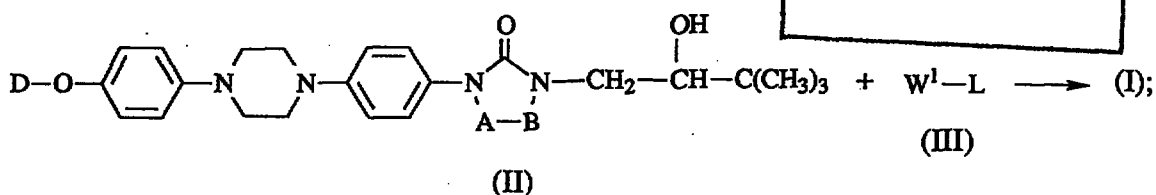




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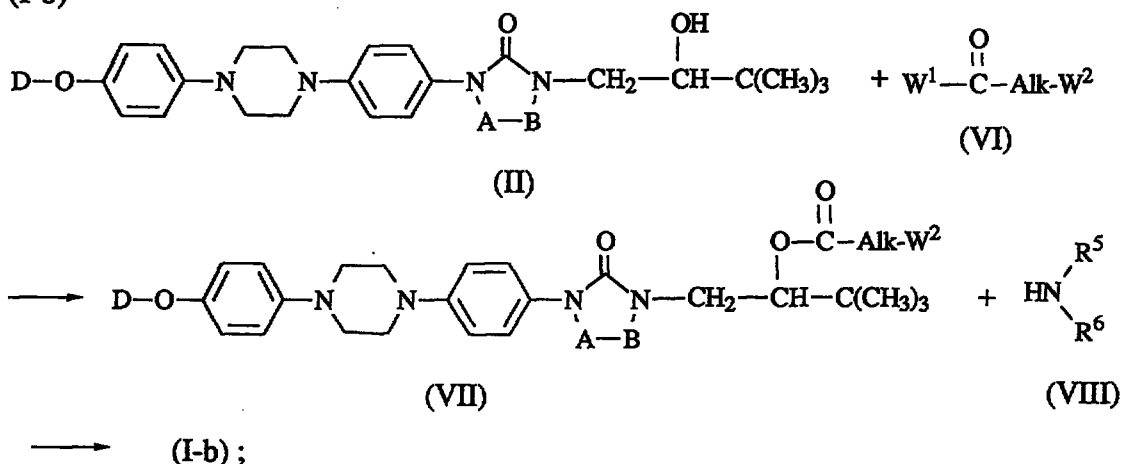


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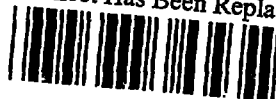
wherein W^1 is a reactive leaving group such as hydroxy or halo, and L is as defined in claim 1; or

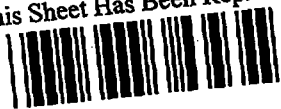
b) O -acylating an intermediate of formula (II) with reagent of formula (VI) wherein W^1 is a reactive leaving group such as hydroxy or halo, and W^2 is a reactive leaving group such as halo or a sulfonyloxy group, and subsequently reacting the thus obtained intermediate (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b)



or converting the compounds of formula (I) into each other following art-known functional group transformation procedures; converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or base; or conversely, converting the salt form into the free base of the free acid by treatment with alkali, respectively an acid; and/or preparing stereochemically isomeric forms thereof.

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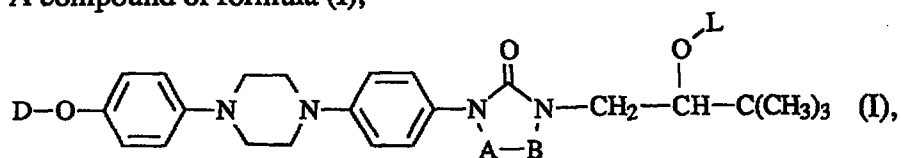


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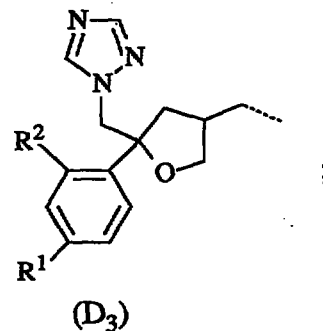
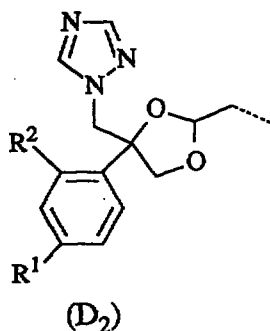
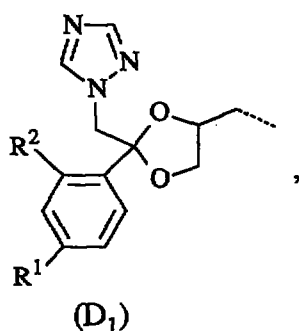
ABSTRACT

WATERSOLUBLE AZOLE ANTIFUNGALS

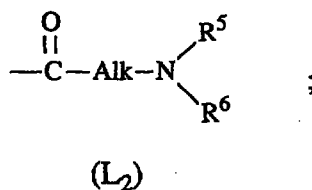
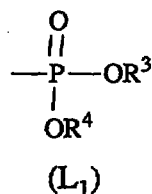
A compound of formula (I),



an acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein A and B taken together form -N=CH-, -CH=N-, -CH₂-CH₂, CH=CH-, -C(=O)-CH₂-, -CH₂-C(=O)-; D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical; R¹ is halo; R² is hydrogen or halo; R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁵ is hydrogen or C₁₋₆alkyl; R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a heterocyclic ring. Active intermediates, compositions and methods of preparing compounds, compositions are described.

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WATERSOLUBLE AZOLE ANTIFUNGALS

The present invention is concerned with novel water-soluble broad-spectrum azole antifungals as well as the antifungally active precursors thereof.

Systemic fungal infections in man are relatively rare in temperate countries and many of the fungi that can become pathogenic normally live commensally in the body or are common in the environment. However, the past few decades have witnessed an increasing incidence of numerous life-threatening systemic fungal infections world-wide and these now represent a major threat to many susceptible patients, particularly those already hospitalized. Most of the increase can be attributed to improved survival of immunocompromised patients and the chronic use of antimicrobial agents. Moreover, the flora typical of many common fungal infections is also changing and this is presenting an epidemiological challenge of increasing importance. Patients at greatest risk include those with impaired immune functioning, either directly as a result of immunosuppression from cytotoxic drugs or HIV infection, or secondary to other debilitating diseases such as cancer, acute leukaemia, invasive surgical techniques or prolonged exposure to anti-microbial agents. The most common systemic fungal infections in man are candidosis, aspergillosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and cryptococcosis.

Antifungals such as ketoconazole, itraconazole and fluconazole are being increasingly employed for the treatment and prophylaxis of systemic fungal infections in immunocompromised patients. However, concern about fungal resistance to some of these agents, especially the more narrow spectrum ones, e.g. fluconazole, is growing. Worse still, it is recognized in the medical world that about 40% of the people suffering from severe systemic fungal infections are hardly able, or not at all to receive medication via oral administration. This inability is due to the fact that such patients are in coma or suffer from severe gastroparesis. Hence the use of insoluble or sparingly soluble antifungals such as itraconazole or saperconazole, that are difficult to administer intravenously, is heavily impeded.

Consequently, there is a need for new antifungals, preferably broad-spectrum antifungals, against which there is no existing resistance and which can be administered

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intravenously. Preferably the antifungal should also be available in a pharmaceutical composition suitable for oral administration. This enables the physician to continue treatment with the same drug after the patient has recovered from his condition which required intravenous administration of said drug.

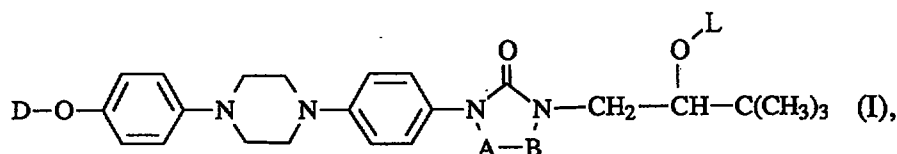
US-4,267,179 discloses heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxymethyl-1,3-dioxolan-2-yl)-methyl-1H-imidazoles and 1H-1,2,4-triazoles useful as antifungal and antibacterial agents. Said patent encompasses itraconazole, which is now available as a broadspectrum antifungal on a world-wide basis.

US-4,916,134 teaches novel 4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-azolylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]triazolones having improved antimicrobial properties. Said patent encompasses saperconazole.

US-4,791,111 discloses derivatives of [[4-[4-(4-phenyl-1-piperazinyl)phenoxy]methyl]-1,3-dioxolan-2-yl]methyl]-1H-imidazoles and 1H-1,2,4-triazoles, structurally related to some of the compounds of the present invention, which are taught to have favourable anti-microbial properties.

US-5,039,676 discloses azole-methyl substituted tetrahydrofurans, structurally related to some of the compounds of the present invention, which are taught to have antifungal activity and EP-0,539,938 teaches analogous trisubstituted tetrahydrofuran antifungals.

The present invention concerns novel compounds of formula



the pharmaceutically acceptable acid or base addition salts thereof and the stereochemically isomeric forms thereof, wherein

A and B taken together form a bivalent radical of formula :

-N=CH- (a),

-CH=N- (b),

-CH₂-CH₂- (c),

-CH=CH- (d),

-C(=O)-CH₂- (e),

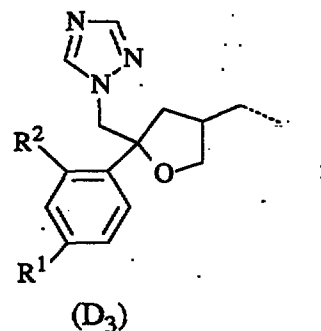
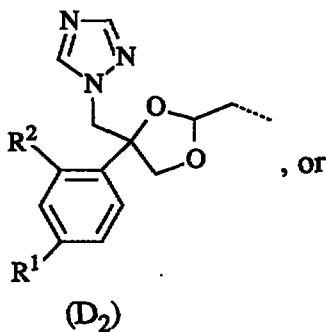
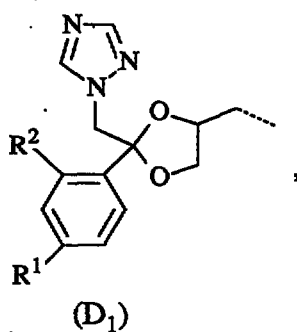
-CH₂-C(=O)- (f),

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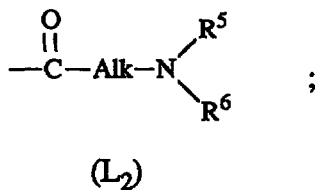
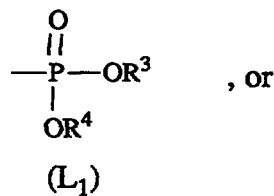
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wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical;

R¹ is halo;

R² is hydrogen or halo;

R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or

R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said substituted piperazine being a piperazine ring substituted on the 4-position of the piperazine ring with C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.

In the definitions hereinabove and hereinafter the term halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl is generic to straight and branch chained hydrocarbons having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and the possible branched isomers thereof; the term "C₁₋₆alkyl" in C₁₋₆alkyloxy,

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aminoC₁₋₆alkyl, mono- and di(C₁₋₆alkyl)aminoC₁₋₆alkyl is as defined hereinabove.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic saturated hydrocarbon radicals, in particular the substituents on the dioxolane or tetrahydrofuran ring, may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

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Alk is appropriately methylene or ethanediyl;

R¹ is suitably fluoro, chloro or bromo, preferably fluoro;

R² is suitably hydrogen, fluoro, chloro or bromo, preferably fluoro;

R³ is suitably hydrogen or phenyl, preferably hydrogen;

R⁴ is suitably hydrogen or phenyl, preferably hydrogen;

R⁵ is suitably hydrogen, methyl or ethyl;

R⁶ is suitably hydrogen, methyl or ethyl; or

R⁵ and R⁶ are suitably taken together with the nitrogen atom to which they are attached to form a pyrrolidine ring or a substituted piperazine ring.

A and B taken together are suitably radicals of formula (a), (b) or (c).

Interesting compounds are those compounds of formula (I) wherein D is a radical of formula (D₁) or (D₂).

Particular compounds are those compounds of formula (I) wherein L is a radical formula (L₂) wherein R⁵ and R⁶ each independently are hydrogen or C₁₋₆alkyl; or when taken together with the nitrogen atom to which they are attached form a pyrrolidine, or a piperazine ring substituted with C₁₋₆alkyl or C₁₋₆alkyloxy on the 4-position of the piperazine ring.

More interesting compounds are those interesting compounds wherein L is a radical of formula (L₁).

Preferred compounds of formula (I) are those compounds of formula (I) wherein D is a radical of formula (D₁), wherein R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula (L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.

The compounds of formula (I) wherein the substituents on the dioxolane or tetrahydrofuran have the cis-configuration, i.e. wherein the triazolmethylene substituent and the substituted phenoxy methylene substituent are on the same side of the plane of the dioxolane or tetrahydrofuran ring, are preferred.

More preferred compounds are selected from :

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate(ester) monohydrate;

(±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(4-fluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate;

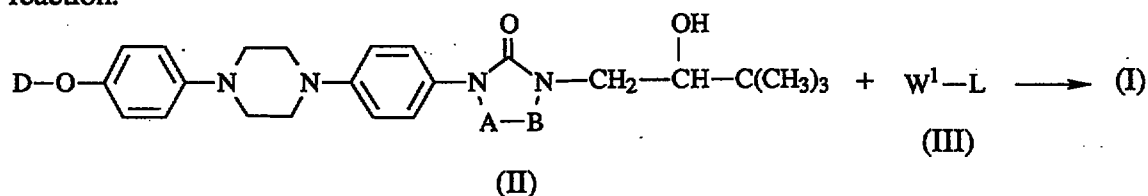
(±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate monohydrochloride; and

(±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate.

Most preferred is

(±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one, the stereochemically isomeric forms thereof and the base addition salts thereof.

The compounds of formula (I) may generally be prepared by Q-acylation or Q-phosphorylation of an intermediate alcohol of formula (II) with an acylating or phosphorylating reagent of formula (III), wherein W¹ is a reactive leaving group such as, hydroxy or halo. Said reaction may be performed following art-known acylation or phosphorylation procedures, for instance, by stirring the reactants in a reaction-inert solvent, optionally in admixture with a base to pick up the acid that is formed during the reaction.

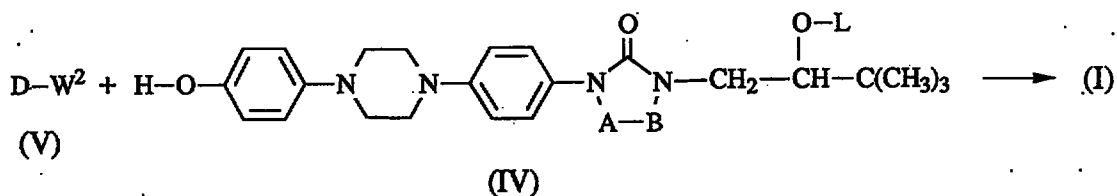


The compounds of formula (I) may also be prepared by Q-alkylating a phenol of formula (IV) with an alkylating reagent of formula (V), wherein W² is a reactive leaving group such as halo, or a sulfonyloxy group. Said reaction may be performed by stirring the

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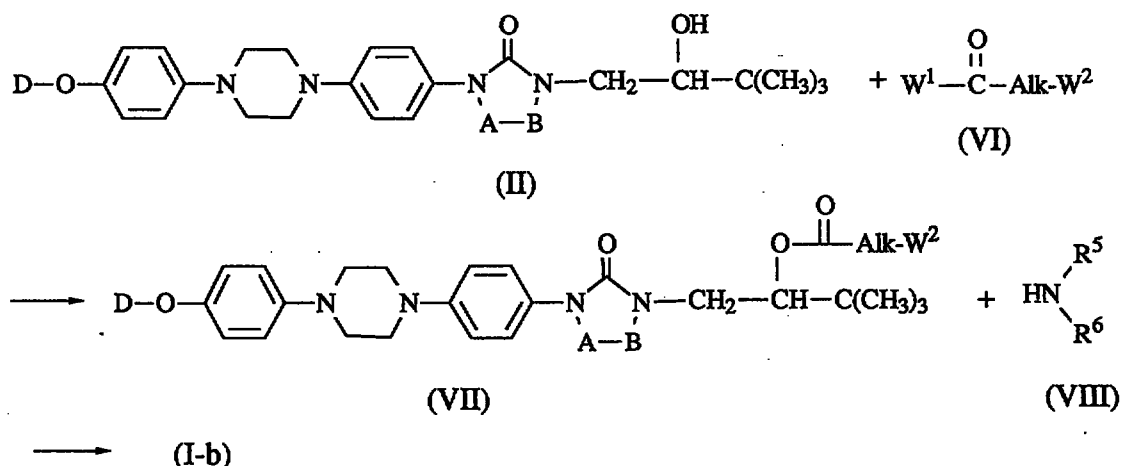
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reactants in a reaction-inert solvent, optionally in admixture with a suitable base to pick up the acid that is formed during the reaction. In the compounds and intermediates mentioned hereinafter the substituents are as defined above, unless otherwise indicated.



The preparation of intermediates of formula (V), wherein D is a radical of formula D₁, has been disclosed in U.S. Patent No 4,267,179. The preparation of intermediates of formula (V), wherein D is a radical of formula D₃, has been disclosed in EP-0,539,938.

The compounds of formula (I), wherein L is a radical of formula L₂, said compounds being represented by formula (I-b), may also be prepared by Q-acylating an intermediate of formula (II) with a reagent of formula (VI) and subsequently reacting the thus obtained intermediate of formula (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b).



The compounds of formula (I) may also be converted into each other following art-known transformations. For instance, the compounds wherein L is a radical of formula L₁, said compounds being represented by formula (I-a), may be interconverted as follows. Compounds of formula (I-a) wherein R³ and/or R⁴ are C₁₋₆alkyl, phenyl or halophenyl may be transformed into compounds of formula (I-a), wherein R³ and/or R⁴ are hydrogen using art-known hydrolysis procedures, e.g. by reaction with sodium hydroxide in an appropriate solvent, e.g. water or 1,4-dioxane.

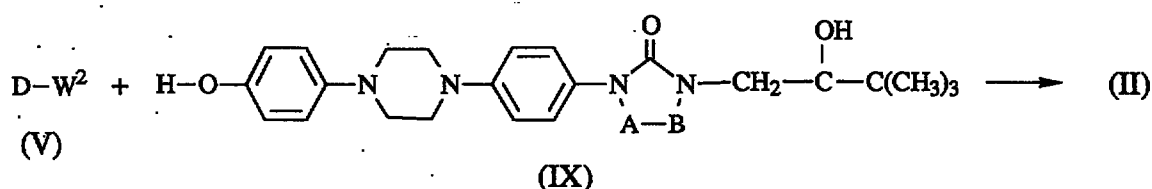
The compounds of formula (I-b) may be interconverted into each other as follows.

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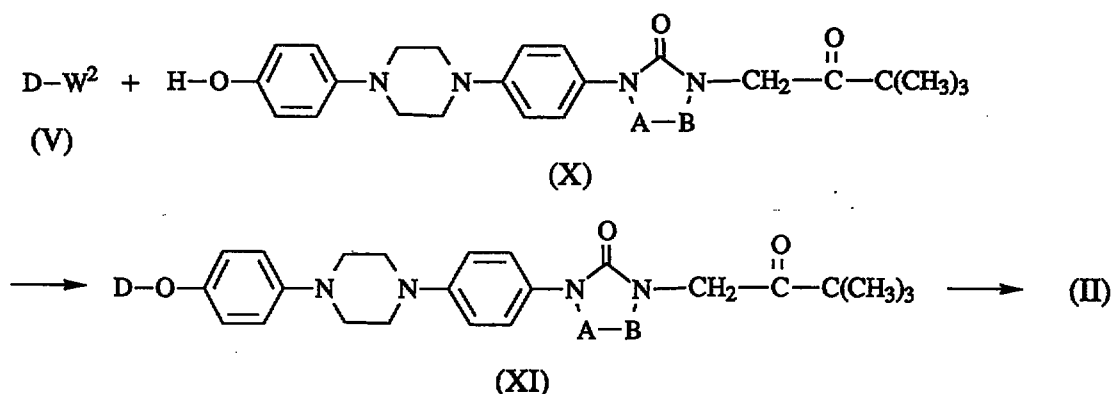
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Compounds of formula (I-b) wherein R^5 and/or R^6 are hydrogen may be transformed into compounds of formula (I-b), wherein R^5 and/or R^6 are C_{1-6} -alkyl, by art-known N-alkylation reactions. Compounds of formula (I-b), wherein R^6 is hydrogen may be converted into compounds of formula (I-b), wherein R^6 is C_{1-6} alkyloxycarbonyl by art-known N-acylation reactions. Conversely compounds of formula (I-b), wherein R^6 is C_{1-6} alkyloxycarbonyl may be converted into compounds of formula (I-b), wherein R^6 is hydrogen by art-known hydrolysis reactions.

The intermediates of formula (II) may be prepared by O-alkylating a reagent of formula (IX) with an alkylating reagent of formula (V) following O-alkylation procedures described hereinabove for the preparation of compounds of formula (I).



The intermediates of formula (II) may also be prepared by O-alkylating a reagent of formula (X) with an alkylating reagent of formula (V) following O-alkylation procedures described hereinabove for the preparation of compounds of formula (I), and subsequently reducing the thus formed intermediate of formula (XI). Said reduction may be performed by stirring the intermediate of formula (XI) with a reducing reagent, such as, for example, sodiumborohydride in a reaction-inert solvent, such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. methanol and mixtures thereof.

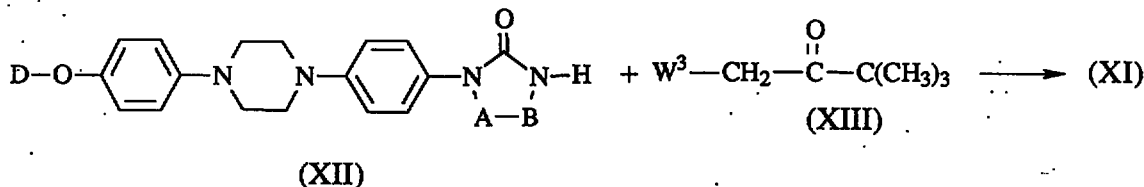


The preparation of intermediates of formula (X) is disclosed in US-4,931,444.

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The intermediates of formula (XI) may also be prepared by N-alkylating an intermediate of formula (XII) following art-known N-alkylation procedures with an alkylating reagent of formula (XIII), wherein W^3 is an appropriate leaving group, e.g. halo.



Pure stereochemically isomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

The compounds of formula (I), the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof are useful agents for combating fungi and bacteria in vivo. Moreover the compounds of formula (I) are soluble in aqueous solutions, which makes them suitable for intravenous administration. Said compounds are found to be active against a wide variety of fungi, such as *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Fonsecaea* sp., *Microsporium canis*, *Paracoccidioides immitis*, *Trichophyton* sp, *Cladosporium carrionii*, and against bacteria such as, for example, *Erysipelotrix insidiosa*, Staphylococci such as *Staphylococcus haemolyticus* and Streptococci such as *Streptococcus pyogenes*.

The intermediates of formula (II), the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof are also useful in treating or

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preventing diseases associated with fungal infections and thus form a further aspect of the present invention. An interesting group of compounds of formula (II) are cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

The present invention also provides compositions for treating or preventing fungal infections comprising an antifungally effective amount of a compound of formula (I) or an intermediate of formula (II) and a pharmaceutically acceptable carrier or diluent.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, e.g. cyclodextrins, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may

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be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Appropriate cyclodextrin derivatives are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxy-butyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkyl-carbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy C_{1-6} alkyl-oxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

Those of skill in treating warm-blooded animals suffering from diseases caused by fungi and/or bacteria could easily determine the effective amount from the test results given herein. In general, it is contemplated that an effective amount would be from 0.01 mg/kg to 50 mg/kg body weight, and more preferably from 0.05 mg/kg to 20 mg/kg body weight.

Experimental part

Of some compounds of formula (I), the absolute stereochemical configuration was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B".

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A. Preparation of the intermediates

Example 1

To a stirred and cooled (ice-bath) mixture of 2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1,2-propanediol (30g), methanesulfonic acid (50ml) and dichloromethane (500ml) was added dropwise 1-bromo-2,2-diethoxyethane (17ml). After stirring for 3 hours at 0°C, the reaction mixture was poured into sodium hydrogen carbonate (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel; CHCl₃/CH₃OH 99:1; CHCl₃/CH₃OH/hexane/CH₃COOC₂H₅ 49:1:20:30). The eluent of the desired fraction was evaporated, yielding 8g (19.0%) of cis-1-[[2-(bromomethyl)-4-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl]-1H-1,2,4-triazole; mp. 76.3°C (interm. 1).

Example 2

A mixture of 2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.01 mol) and sodium hydride (0.012 mol) in N,N-dimethylformamide (100ml) was stirred under nitrogen at 70°C. Intermediate (1) (0.012 mol) was added and the mixture was stirred further overnight. Intermediate (1) (2g) was added again and the mixture was stirred at 70°C for 6 hours and then at room temperature overnight. The mixture was evaporated, the residue was taken up in dichloromethane and washed. The organic layer was dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/hexane/ethyl acetate 50/20/30). The pure fractions were collected and evaporated. The residue was purified further on a glass filter over silica gel/NH₂ (eluent: CH₂Cl₂). The pure fractions were collected and evaporated. The residue was crystallized from ethyl acetate, yielding 2.2g (31%) of (±)-cis-4-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; 197.1°C (interm. 2).

Example 3

a) A mixture of cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol (0.2mol) in pyridine (400ml) and dichloromethane (250ml) was stirred at room temperature. A solution of 4-cyanobenzoyl chloride (0.22mol) in dichloromethane (150ml) was added dropwise. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from methylbenzene. The crystals were filtered off and dried.

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This fraction was purified by column chromatography over a Chiracell OD column (eluent: C₂H₅OH). The first peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.2g (24.9%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl 4-cyanobenzoate; mp. 146.3°C; $[\alpha]_D^{20} = +22.71^\circ$ (c = 0.5% in methanol) (interm. 3). The second peak fractions were combined and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 21.4g (25.1%) (-)-cis-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methyl 4-cyanobenzoate; mp. 144.0°C; $[\alpha]_D^{20} = -22.64^\circ$ (c = 0.5% in methanol) (interm. 4).

b) A mixture of intermediate (3) (0.049mol) and sodium hydroxide 50% (0.059mol) in water (300ml) and 1,4-dioxane (300ml) was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was partitioned between water and dichloromethane. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The crystals were filtered off and dried, yielding 10.1g (70%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.0°C; $[\alpha]_D^{20} = +16.58^\circ$ (c = 0.5% in methanol) (interm. 5)

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; mp. 123.2°C; $[\alpha]_D^{20} = -15.97^\circ$ (c = 0.5% in methanol) (interm. 6).

c) A mixture of intermediate (5) (0.02mol) and N,N-diethylethanamine (0.03mol) in dichloromethane (50ml) was stirred at room temperature. Methanesulfonyl chloride (0.03mol) was added dropwise and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated. The residue was partitioned between methylbenzene and water. A precipitate was formed, which was filtered off, dried and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding two fractions. Those fractions were combined and recrystallized from 2,2'-oxybispropane / 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 40°C), yielding 5.88g (78.3%) of (+)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate(ester); $[\alpha]_D^{20} = +15.50^\circ$ (c = 0.2% in methanol) (interm. 7).

In a similar manner was also prepared :

(-)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methanesulfonate (ester); $[\alpha]_D^{20} = -14.50^\circ$ (c = 0.2% in methanol) (interm. 8).

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Example 4

- a) A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.046mol), 2-(chlorodimethylsilyl)-2-methylpropane (0.063mol) and 1H-imidazole (0.19mol) in *N,N*-dimethylformamide (300ml) was stirred for 4 hours at 50°C. The reaction mixture was poured out into water. The resulting precipitate was filtered off and dried, yielding 21g (83%) of product. A sample (1g) was triturated in 2,2'-oxybispropane, filtered off and dried, yielding 0.7g of (±)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one; mp. 196.1°C (interm. 9).
- b) Intermediate (9) (0.036mol, mixture of enantiomers) was separated in its enantiomers by column chromatography over a Chiracell® OD column (eluent: n-hexanes/2-propanol 65/35). The fraction, corresponding to a first chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 1.56g (7.8%) of (-)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 10). The fraction, corresponding to a second chromatographic peak, was collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried (vacuum; 50°C); yielding 2.28g (11.4%) of (+)-4-[4-[4-[4-[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-1-piperazinyl]phenyl]-2-(2-hydroxy-3,3-dimethylbutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (interm. 11).
- c) A mixture of intermediate (10) (0.0135mol) in dichloromethane (150ml) was stirred until complete dissolution. A solution of tetrabutylammonium fluoride in tetrahydrofuran (0.015mol) was added in one portion and the reaction mixture was stirred for 1 hour at room temperature. The mixture was diluted with water (150ml) and stirred for 1 hour. The precipitate was filtered off and recrystallized from 2-methoxyethanol. The product was filtered off and dried (vacuum; 60°C), yielding 4.7g (79.6%) of (-)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = -3.14^\circ$ (c = 0.1% in *N,N*-dimethylformamide) (interm. 12).

In a similar manner was also prepared :

- (+)-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one; $[\alpha]_D^{20} = +6.22^\circ$ (c = 0.1% in *N,N*-dimethylformamide) (interm. 13).

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Example 5

A mixture of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (9.3g), 1-bromo-3,3-dimethyl-2-butanone (2.8g), sodium carbonate (6.4g) and 1,3-dimethyl-2-imidazolidinone (52.2g) was stirred for 5 hours at 100°C. After cooling, the reaction mixture was poured into water. The formed precipitation was filtered off and dissolved in dichloromethane. This solution was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 5.5g (51.3%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2-(3,3-dimethyl-2-oxobutyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.; mp. 176.2°C (interm. 14).

Example 6

To a mixture of intermediate (14) (4.5g), 1,4-dioxane (40ml) and methanol (3ml) was added dropwise a solution of sodium tetrahydroborate (0.3g) in some water. After stirring overnight, the reaction mixture was poured into water and acidified with acetic acid to $\pm$ pH 5. The precipitate was filtered off, washed with water, dried and purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanol, yielding 2.2 g (48.7%) of cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 196.4°C (interm. 15).

Example 7

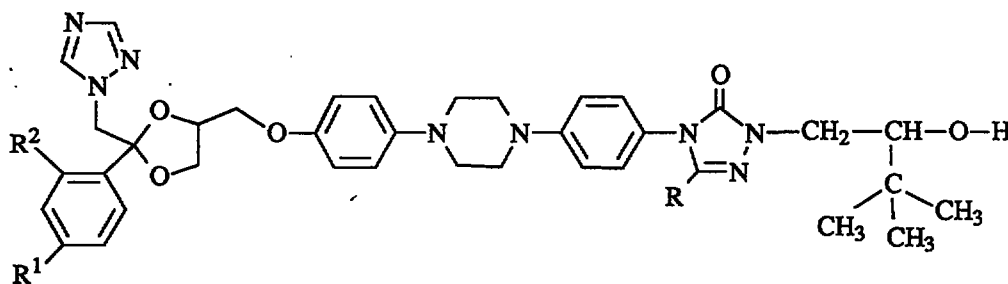
Sodium hydride (0.00675mol) was added portionwise to a mixture of intermediate (12) (0.00595mol) in N,N-dimethylformamide (50ml), stirred at room temperature. The mixture was stirred for 90 minutes at room temperature. Intermediate (7) (0.0054mol) was added and the reaction mixture was stirred for 4 hours at 60°C. The mixture was cooled and the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over an aminopropyl column (eluent: CH₂Cl₂/CH₃OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 4-methyl-2-pentanone. The precipitate was filtered off and dried (vacuum; 50°C), yielding 1.67g (43.1%) of

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(+)-[cis(+)(B)]-4-[4-[4-[4-[(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 191.9°C; $[\alpha]_D^{20} = +12.03^\circ$ (c = 0.5% in dichloromethane) (interm.20).

Table 1



Int. No.	Ex. No.	R	R ¹	R ²	Physical data
15	6	H	F	F	mp. 196.4°C / cis
16	6	H	Cl	Cl	mp. 187.1°C / cis
17	6	H	Cl	H	mp. 201.5°C / cis
18	6	H	F	H	mp. 213.2°C / cis
19	6	H	F	H	mp. 211.1°C / trans
20	7	H	F	F	mp. 191.9°C / $[\alpha]_D^{20} = +12.03^\circ$ (c = 0.5% in dichloromethane) / (+)-[cis(+)(B)]
21	7	H	F	F	mp. 213.2°C / $[\alpha]_D^{20} = -7.89^\circ$ (c = 0.5% in dichloromethane) (-)-[cis(-)(B)]
22	7	H	F	F	mp. 212.5°C / $[\alpha]_D^{20} = +8.38^\circ$ (c = 0.5% in dichloromethane) (+)-[cis(+)(A)]
23	7	H	F	F	mp. 185.6°C / $[\alpha]_D^{20} = -5.08^\circ$ (c = 0.5% in N,N-dimethylformamide) (-)-[cis(-)(A)]

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Example 8

A mixture of intermediate (2) (0.0025 mol) in dichloromethane (100ml) and methanol

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(100ml) was stirred at room temperature. Sodium borohydride (0.005 mol) was added and the mixture was stirred for 4 hours. Water (100ml) was added, the mixture was stirred overnight and separated. The organic layer was washed, dried, filtered off and evaporated. The residue was crystallized from ethyl acetate, yielding 1.6g (89.3%) of (±)-cis-4-[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 184.1°C (interm. 24).

Example 9

A mixture of 2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0035 mol), cis-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanmethanol 4-methylbenzene-sulfonate (the preparation of which is described in European Patent Application 0,539,938) (0.0033 mol) and sodium hydroxide (0.01 mol) in N,N-dimethylformamide (50ml) was stirred under nitrogen at 50°C for 4 hours and the mixture was stirred further under nitrogen at 60°C for 2 hours. The mixture was cooled and water was added. The product was crystallized out, filtered off and dried. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/ CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was recrystallized from dioxane/2,2'-oxybispropane, yielding 1.7g (72%) of (±)-cis-4-[4-[4-[4-[[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one; mp. 210.8°C (interm. 25).

Example 10

Chloroacetyl chloride (0.02 mol) was added to a stirring mixture of intermediate (15) (0.0082 mol) in dichloromethane (100ml). Pyridine (0.037 mol) was added dropwise and the mixture was stirred for 2 hours. Hydrochloric acid 1N (50ml) was added, the mixture was stirred for 2 hours and separated. The organic layer was washed with a sodium hydrogen carbonate-solution, dried, filtered off and evaporated. The residue was crystallized and triturated in 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 6.3g (96.8%) of product. A sample (1g) was recrystallized from 4-methyl-2-pentanone, yielding 0.6g of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl chloroacetate (interm. 26).

Example 11

A mixture of (±)-2,4-dihydro-4-(2-hydroxy-3,3-dimethylbutyl)-2-[4-[4-(4-hydroxy-

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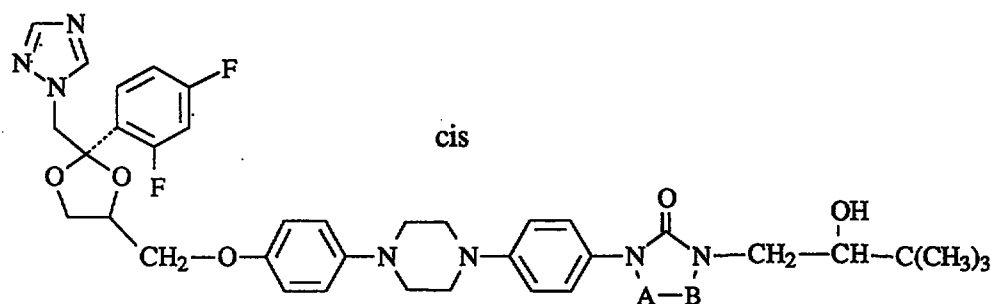
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phenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-one (0.0068 mol), (±)-cis-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol methane-sulfonate (ester) (0.0082 mol) and sodium hydroxide (0.025 mol) in *N,N*-dimethylformamide (100ml) was stirred under nitrogen at 60°C for 4 hours. The mixture was cooled, water was added and the mixture was stirred. The precipitate was filtered off and dried. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH/ethyl acetate/n-hexane 48/2/30/20). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone, yielding 1.1g (22%) of (±)-cis-2-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(2-hydroxy-3,3-dimethyl-butyl)-3H-1,2,4-triazol-3-one; mp. 201.2°C (interm. 27).

Example 12

A mixture of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(3,3-dimethyl-2-oxobutyl)-1,3-dihydro-2H-imidazol-2-one (0.0036 mol) in methanol (50ml) and dichloromethane (50ml) was stirred. Sodium borohydride (0.01 mol) was added and the mixture was stirred at room temperature for 1 hour. Water (100ml) was added and the mixture was stirred for 1 hour. The mixture was separated and the aqueous layer was extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone, yielding 1.9g (73%) of (±)-cis-1-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(2-hydroxy-3,3-dimethylbutyl)-2-imidazolidinone; mp. 196.8°C (interm. 29).

Table 2



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Interm. No.	Ex. No.	A-B	Physical data
27	11	-N=CH-	mp. 201.2°C
28	11	-(C=O)-C(CH ₃) ₂ -	mp. 141.8°C
29	12	-CH ₂ -CH ₂ -	mp. 196.8°C
30	11	-CH=N	mp. 147.6°C / (+)-[(B-cis), B] / $[\alpha]_D^{20}$ = +1.20° (c = 0.5% in methanol) /

B. Preparation of the final compounds

Example 13

A mixture of intermediate (15) (0.0014 mol), diphenyl chlorophosphate (0.003 mol) and *N,N*-dimethyl-4-pyridinamine (1g) in dichloromethane (30ml) was stirred at room temperature for 2 hours. The mixture was purified on a glass filter over silica gel (eluent: CH₂Cl₂ / CH₃OH 98/2). The pure fractions were collected and evaporated. The residue was recrystallized from 4-methyl-2-pentanone/2,2'-oxybispropane, yielding 1.1g (83%) (±)-*cis*-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate; mp. 170.8°C (comp. 1).

Example 14

A mixture of compound (1) (0.0029 mol) and a dispersion of sodium hydroxide 50% solution (5g) in 1,4-dioxane (50ml) was stirred at room temperature for 6 hours. Water (200ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid till pH = 2-3. The mixture was extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was dissolved in a saturated sodium hydrogen carbonate solution (100ml), washed with 2,2'-oxybispropane and extracted twice with dichloromethane (500ml) and methanol (100ml). The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 2-propanol and a little water, yielding 1.2g (46%) of (±)-*cis*-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phenyl sodium phosphate; mp. 167.0°C (comp. 2).

Example 15

A mixture of compound (1) (0.0038 mol) and sodium hydroxide 50% solution (5g) in

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1,4-dioxane (100ml) was stirred at room temperature overnight. Water (600ml) was added, the mixture was filtered over dicalite and the filtrate was acidified with hydrochloric acid. The precipitate was filtered off (*) and the filtrate was extracted with dichloromethane. The mixture was evaporated. The residue, the precipitate (*) and sodium hydroxide 50% (5g) were stirred at 60°C for 24 hours. Sodium hydroxide 50% (3g) was added again and the mixture was stirred at 60°C for 48 hours. The mixture was cooled, acidified with hydrochloric acid 1N till pH=4 and extracted with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was boiled up in methanol (70ml), filtered off and methanol/ammonia (20ml) was added to the filtrate. The mixture was boiled up in 2-propanol (20ml) and cooled. The mixture was filtered off, the precipitate was dissolved in water (200ml) and washed twice with ethyl acetate. The aqueous layer was acidified with hydrochloric acid 1N and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was dissolved in methanol (70ml) and methanol/ammonia (10ml) was added. The precipitate was filtered off and dried, yielding 1.6g (51%) of (±)-ammonium cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl phosphate; mp. 189.6°C (comp. 3).

Example 16

Sodium hydroxide 50% (1.4 mol) was added to a suspension of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl diphenyl phosphate (0.07 mol) in 1,4-dioxane (1400 ml) under N₂ flow. The resulting suspension was heated to 60 °C. The reaction solution was stirred for 92 hours at 60 °C. The mixture was allowed to cool to 25 °C. The mixture was poured out into distilled water (5.25 liter) and this mixture was stirred vigorously for 1 hour. The mixture was filtered. The filtrate was acidified (pH = 2.7) with hydrochloric acid and recipitation resulted. The aqueous layer was extracted with CH₂Cl₂ (1 x 2 liter; 1 x 1.5 liter). The combined extracts were dried (Na₂SO₄), filtered and the solvent was evaporated. The residue (71.02 g; 124.7% yield) was stirred in 2-propanol (1050 ml), heated to reflux temperature, stirred and refluxed for 5 min, cooled on an ice bath while stirring vigorously, cooled to 20 °C and stirring was continued overnight. The precipitate was filtered off, washed with 2-propanol (1 x 35 ml), diisopropylether (2 x 35 ml) and dried (vacuum; 50 °C), yielding 48.10 g of (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-

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yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one hemihydrate; mp. 156.2°C (comp. 17).

Example 17

1-Deoxy-1-(methylamino)-D-glucitol (0.02 mol) was added to a mixture of compound (17) (0.005 mol) in water (70 ml) and the mixture was stirred until complete dissolution (30 min). The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. Ethanol (250 ml) was added and the mixture was stirred vigorously. The mixture was cooled on an ice bath and stirred for 1 hour and precipitation resulted. The mixture was allowed to warm to room temperature (20 °C). The mixture was stirred for 18 hours at room temperature and the resulting precipitate was filtered off, washed with ethanol, with diisopropylether (2 x 10 ml) and dried (vacuum; 50 °C), yielding: 6.14 g (1). The filtrate was evaporated. The residue was dried (vacuum; 50 °C), yielding: 1.98 g (2). Fraction (1) was ground, stirred vigorously for 5 hours in ethanol (200 ml) and the resulting precipitate was filtered off, washed with ethanol (4 x 5 ml) and dried (vacuum; 45-50 °C; 64 hours), yielding: 4.98 g (±)-cis-4-[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one 1-deoxy-1-(methylamine)-D-glucitol (1:2).monohydrate (comp. 18)

Example 18

A mixture of intermediate (26) (0.0025 mol) and pyrrolidine (0.014 mol) in *N,N*-dimethylformamide (50ml) was stirred at room temperature for 4 hours. Water was added and the mixture was stirred. The precipitate was filtered off, washed with water and purified on a glass filter over silica gel (eluent 1: CH₂Cl₂/CH₃OH 98/2 and eluent 2: CH₂Cl₂/CH₃OH 95/5). The suitable fractions were collected and evaporated. The residue was dissolved in dichloromethane (100ml) and stirred with hydrochloric acid 0.4N (50ml). The mixture was separated and the aqueous layer was extracted four times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The oily residue was dissolved in dichloromethane, washed with a sodium hydrogen carbonate solution, dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone, yielding 1.1 g (53%) of (±)-cis-1-[[4-[4-[4-[4-[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 1-pyrrolidineacetate; mp. 156.7°C (comp. 28).

Example 19

A mixture of intermediate (16) (0.0066 mol), 4-methyl-1-piperazineacetic acid dihydrochloride (0.013 mol), 1,3-dicyclohexylcarbodiimide (0.026 mol) and *N,N*-

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dimethyl-4-pyridinamine (0.026 mol) in dichloromethane (100ml) was stirred at room temperature for 4 hours. Hydrochloric acid 1N (200ml) was added and the mixture was stirred for 1 hour. The precipitate was filtered off, water (600ml) was added and the mixture was separated (*). The aqueous layer was washed with dichloromethane (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 4.5g of fraction 1. (*) The organic layer was washed with hydrochloric acid 1N (100ml) and separated. The aqueous layer was neutralized with pyridine and extracted twice with dichloromethane. The combined organic layers were dried, filtered off and evaporated, yielding 2g of fraction 2. Fractions 1 and 2 were put together and recrystallized from (acetonitrile 2% water)/ 2,2'-oxybispropane, yielding 3.8g (61%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl 4-methyl-1-piperazineacetate . monohydrochloride . hemihydrate; mp. 156.0°C (comp. 32).

Example 20

A mixture of compound (17) (0.0034 mol) in a solution of hydrochloric acid in 2-propanol (10ml) and dichloromethane (60ml) was stirred and refluxed for 30 minutes. The mixture was evaporated. The residue was dissolved in water and filtered off. The filtrate was neutralized with a sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (50ml) and washed three times with ethyl acetate (100ml). The aqueous layer was neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from acetonitrile and a little N,N-dimethylformamide, yielding 1.3g (46%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropyl β-alanine monohydrochloride; mp. 217.9°C (comp. 36).

Example 21

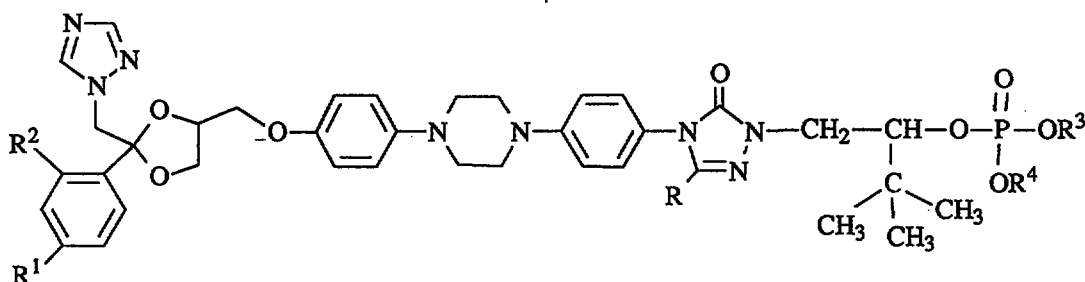
A mixture of (±)-cis-N-[1-[3-[1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethylpropoxy]-3-oxopropyl]-1,4-dihydro-4-pyridinylidene]-N-methylmethanaminium chloride monohydrate (0.0024 mol) and pyrrolidine (0.01 mol) in N,N-dimethylformamide (50ml) was stirred at room

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temperature for 1 hour. The mixture was poured into water and extracted three times with dichloromethane. The combined organic layers were washed with water, dried, filtered off and evaporated. The residue was dissolved in hydrochloric acid 0.5N (500ml) and washed three times with ethyl acetate (100ml). The aqueous layer was neutralized with pyridine and extracted three times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (0.5ml). The residue was purified on a glass filter over silica gel (eluent : CH₂Cl₂/CH₃OH 96/4). The suitable fractions were collected and evaporated. The residue was dissolved in hydrochloric acid 1N (50ml), neutralized with pyridine and extracted five times with dichloromethane. The combined organic layers were dried, filtered off and evaporated. The residue was crystallized from 4-methyl-2-pentanone and water (5 drops), yielding 1.1g (51%) of (±)-cis-1-[[4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]methyl]-2,2-dimethyl-propyl 1-pyrrolidinepropanoate . monohydrochloride . monohydrate; mp. 154.4°C (comp. 37)

Table 3



Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
1	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 170.8°C
2	14	H	F	F	H	C ₆ H ₅	mp. 167.0°C / Na ⁺
3	15	H	F	F	H	H	mp. 189.6°C / NH ₄ ⁺
4	13	H	Cl	Cl	C ₆ H ₅	C ₆ H ₅	mp. 167.1°C
5	15	H	Cl	Cl	H	H	mp. 188.2°C / NH ₄ ⁺
6	13	H	Cl	H	C ₆ H ₅	C ₆ H ₅	mp. 174.2°C
7	15	H	Cl	H	H	H	mp. 195.5°C / NH ₄ ⁺
8	13	H	F	H	C ₆ H ₅	C ₆ H ₅	mp. 184.6°C
9	15	H	F	H	H	H	mp. 159.8°C / NH ₄ ⁺

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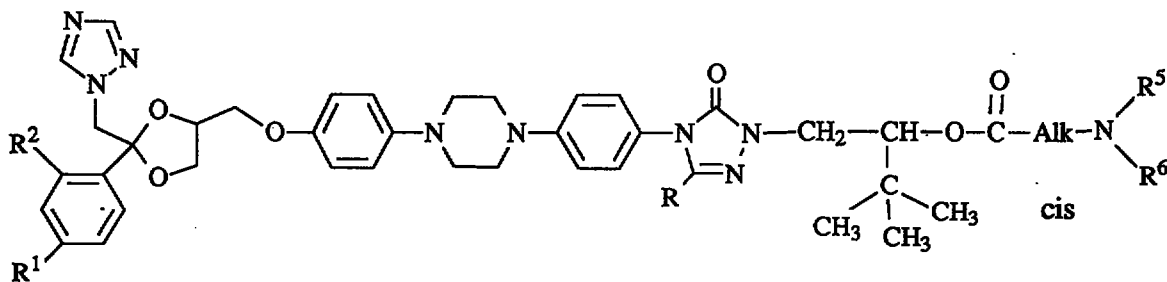
Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
10	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 147.6°C [α] _D ²⁰ = +1.20° (c = 0.5% in methanol) (+)-[(B-cis), B]
11	15	H	F	F	H	H	mp. 200.7°C / NH ₄ ⁺ [α] _D ²⁰ = -15.8° (c = 0.1% in DMF) (+)-[(B-cis), B]
12	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.6°C [α] _D ²⁰ = -15.89° (c = 0.1% in methanol) (-)-[(A-cis), B]
13	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 76.7°C [α] _D ²⁰ = 13.62° (c = 0.1% in methanol) (-)-[(B-cis), A]
14	13	H	F	F	C ₆ H ₅	C ₆ H ₅	mp. 145.7°C [α] _D ²⁰ = -3.52° (c = 0.1% in methanol) (-)-[(A-cis), A]
15	13	H	F	F	C ₆ H ₅	C ₆ H ₅	cis
16	15	H	F	F	H	H	mp. 201.3°C / NH ₄ ⁺ cis
17	16	H	F	F	H	H	mp. 156.2°C cis 1/2 H ₂ O
18	17	H	F	F	H	H	mp. 117.6°C cis .2 CH ₃ -NH-CH ₂ -(C-OH) ₄ -CH ₂ -OH
19	17	H	F	F	H	H	mp. 184.7°C / cis C(CH ₂ -OH) ₃ NH ₂
20	17	H	F	F	H	H	mp. 251.7°C / .2 Na ⁺ cis. 7/2 H ₂ O

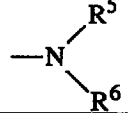
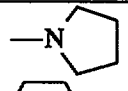
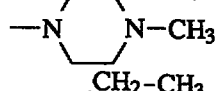
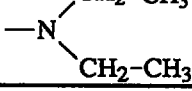
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Co. No.	Ex. No.	R	R ¹	R ²	R ³	R ⁴	Physical data
21	15	H	F	F	H	H	mp. 202.7°C / NH ₄ ⁺ / [α] _D ²⁰ = 51.72° (c = 0.5% in DMF) / (-)[(B-cis),A]
22	15	H	F	F	H	H	[(A-cis),A]
23	16	H	F	F	H	H	mp. 171.6°C / [α] _D ²⁰ = +10.93° (c = 0.5% in DMF)
24	16	H	F	F	H	H	[(B-cis),A] . H ₂ O
25	16	H	F	F	H	H	NH ₄ ⁺ / [(A-cis),B]
26	16	H	F	F	H	H	mp. 167.8°C / [α] _D ²⁰ = +12.59° (c = 1% in DMF)
27	15	H	F	F	H	H	[α] _D ²⁰ = 3.70° (c = 0.5% in methanol)

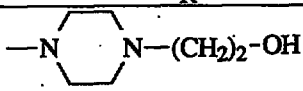
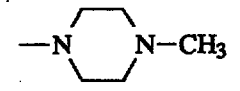
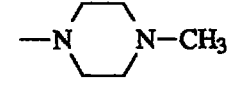
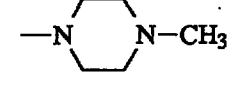
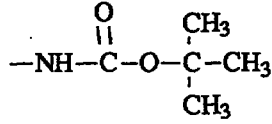
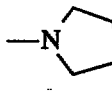
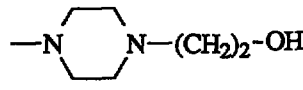
Table 4



Co. No.	Ex. No.	R	R ¹	R ²	Alk		Physical data
28	18	H	F	F	CH ₂		mp. 156.7°C
29	18	H	F	F	CH ₂		mp. 155.3°C
30	18	H	F	F	CH ₂		mp. 166.3°C

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Co. No.	Ex. No.	R	R ¹	R ²	Alk	$\begin{array}{c} \text{R}^5 \\ \\ -\text{N} \\ \\ \text{R}^6 \end{array}$	Physical data
31	18	H	F	F	CH ₂		mp. 171.7°C .2HCl.H ₂ O
32	19	H	Cl	Cl	CH ₂		mp. 156.0°C .2HCl.1/2H ₂ O
33	19	H	F	F	CH ₂ -CH ₂		mp. 213.7°C .HCl
34	19	H	F	F	CH ₂		mp. 201.5°C .HCl
35	19	H	F	F	CH ₂ -CH ₂		-
36	20	H	F	F	CH ₂ -CH ₂	NH ₂	mp. 217.9°C .HCl
37	21	H	F	F	CH ₂ -CH ₂		mp. 154.4°C .HCl.H ₂ O
38	21	H	F	F	CH ₂	NH ₂	mp. 219.5°C .HCl
39	21	H	F	F	CH ₂ -CH ₂		mp. 208.5°C .2HCl

C. Physicochemical example

Example 22

Solubility

An excess of compound was added to 5 ml of solvent (the type of solvent is specified in the table). The mixture was shaken during 1 hour at room temperature. The precipitate was filtered off. The pH of the remaining solvent was measured and is shown in the table. The concentration of the compound was measured via UV-spectroscopy and is shown in the column "Solubility".

Co. No.	Solvent	pH	Solubility (mg/ml)
2	water	7.01	> 6
3	water	6.95	31.93
7	water	6.80	0.35

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Co. No.	Solvent	pH	Solubility (mg/ml)
9	water	6.65	2.65
29	0.1 N HCl	1.62	4.89
30	0.1 N HCl	1.65	5.22
33	0.1 N HCl	1.65	> 6
34	0.1 N HCl	1.75	> 6
36	0.1 N HCl	1.25	> 6
37	0.1 N HCl	1.26	> 6
38	0.1 N HCl	1.59	> 6
31	0.1 N HCl	1.53	> 6

D. Pharmacological examples

Example 23

Mouse triple mycosis model

The test compounds were evaluated for their activity in a mouse model of fungal infection in which three mycoses - vaginal candidosis, cutaneous trichophytosis and disseminated aspergillosis - were established simultaneously. The mice, in groups of 10, were pretreated with subcutaneous injections of oestradiol valerate (500µg) then inoculated on day 0 with the following : 100 000 colony forming units (CFU)/g of *Aspergillus fumigatus* B19119 intravenously, a suspension containing 10^8 *Candida albicans* cells intravaginally and a aqueous suspension of *Trichophyton quinckeanum* on lightly scarified dorsal skin. Treatment with the test compounds (orally or intravenously) was begun on the day of infection and continued for 5 days. All animals that died spontaneously and those that survived and were sacrificed on day 6, were sampled for the numbers of *Aspergillus fumigatus* CFU/g in kidney and spleen, for skin lesion scores (0 = no visible lesion; 1 = a few point lesions; 2 = moderate lesions; 3 = severe lesions) and for *Candida albicans* CFU from a vaginal swab.

Mouse disseminated *Candida* model

Mice in groups of 10 were infected intravenously with 8×10^5 CFU of *Candida albicans*. Treatment was begun on the day of infection and repeated daily for 9 days. *Candida albicans* CFU/g kidney were measured for all mice that died spontaneously or were killed on day 10.

The table indicates the lowest concentrations of the shown compounds that achieved a reduction in mean *Candida* counts of 1 log (i.e. a 10-fold reduction) or more, either in

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the triple mycosis model or the disseminated *Candida* infection; also the lowest concentrations that reduced mean skin scores below 1.0 in the cutaneous dermatophytosis component of this model (NT = not tested, IV = intravenous).

CN	Mouse triple mycosis model				Mouse disseminated <i>Candida</i> model
	Vaginal <i>Candida</i> CFU reduced by 1 log or more		Dermatophyte skin score reduced to ≤ 1		Kidney <i>Candida</i> CFU reduced by 1 log or more
	IV route	oral route	IV route	oral route	IV route
34	2.5	2.5	2.5	2.5	5
3	2.5	2.5	2.5	2.5	10
17	< 2.5	NT	< 2.5	NT	NT

Example 24

Determination of fungal susceptibility.

A panel of *Candida* isolates plus single isolates of the dermatophytes *Microsporum canis*, *Trichophyton rubrum* and *T. mentagrophytes*; *Aspergillus fumigatus*, and *Cryptococcus neoformans* were used to evaluate the activity of the test compounds in vitro. Inocula were prepared as broth cultures (yeasts) or as suspensions of fungal material made from agar slope cultures (moulds). The test compounds were pipetted from DMSO stock solution into water to provide a series of 10-fold dilutions. The fungal inocula were suspended in the growth medium CYG (F.C. Odds, Journal of Clinical Microbiology, 29, (2735-2740, 1991) at approximately 50000 colony-forming units (CFU) per ml and added to the aqueous test drugs.

The cultures were set up in the 96 wells of plastic microdilution plates and they were incubated for 2 days at 37°C (*Candida* spp.) or for 5 days at 30°C (other fungi). Growth in the microcultures was measured by its optical density (OD) measured at a wavelength of 405 nm. The OD for cultures with test compounds was calculated as a percentage of the control, drug-free OD. Inhibition of growth to 35% of control or less was recorded as significant inhibition.

Minimal inhibitory concentration (MICs) of intermediates 15, 16, 17, 18, 24 range from ≤ 0.01 to about 10 μM *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, non-azole-resistant *Candida albicans*, *Candida kefyr*, *Microsporum canis*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, *Aspergillus fumigatus*.

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E. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 25 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of a sodium hydroxide solution and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I.. The resulting solution was filled into suitable containers.

Example 26 : CAPSULES

20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

Example 27 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10,000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

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Example 28 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams sodium hydroxide were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Example 29 : SUPPOSITORIES

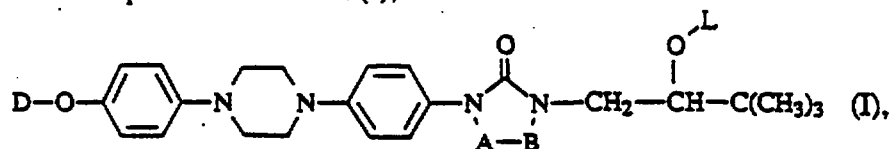
3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.



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CLAIMS

1. A compound of formula (I),



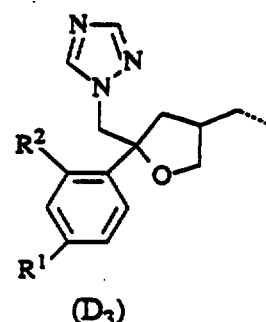
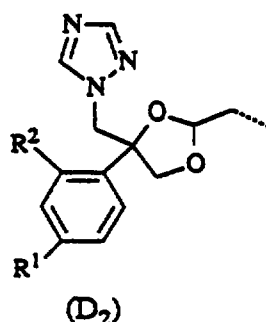
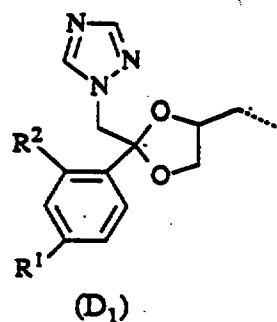
a pharmaceutically acceptable acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein

A and B taken together form a bivalent radical of formula :

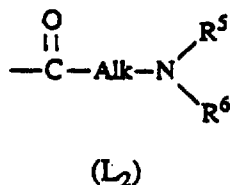
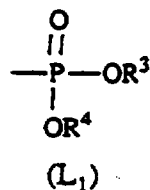
- N=CH- (a),
- CH=N- (b),
- CH₂-CH₂- (c),
- CH=CH- (d),
- C(=O)-CH₂- (e),
- CH₂-C(=O)- (f),

wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆-alkyl-radical;

D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical;



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R¹ is halo;

R² is hydrogen or halo;

R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl;

R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or

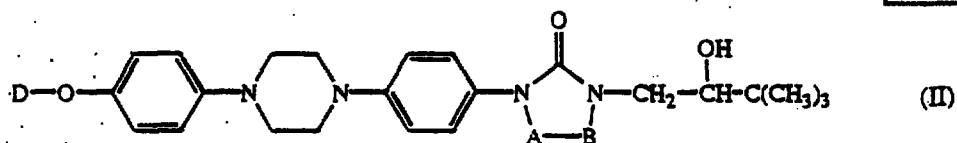
R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, morpholine, piperazine or substituted piperazine ring, said substituted piperazine being a piperazine ring substituted on the 4-position of the piperazine ring with C₁₋₆alkyl, hydroxyc₁₋₆alkyl, aminoc₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoc₁₋₆alkyl.

2. A compound according to claim 1, wherein D is a radical of formula (D₁) or (D₂).
3. A compound according to claim 2, wherein D is a radical of formula (D₁), wherein R¹ is chloro or fluoro and R² is hydrogen, chloro or fluoro; L is a radical of formula (L₁), wherein R³ and R⁴ each independently are phenyl or hydrogen.
4. A compound according to claim 3, wherein the compound is (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2-[3,3-dimethyl-2-(phosphonooxy)butyl]-2,4-dihydro-3H-1,2,4-triazol-3-one, a stereochemically isomeric form or a base addition salt form thereof.
5. A composition comprising a pharmaceutically acceptable carrier and as active ingredient an antifungally effective amount of a compound as claimed in any of claims 1 to 4.
6. A process for preparing a composition as claimed in claim 5 characterized in that a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
7. Use of a compound according to claims 1 to 4 for the manufacture of a medicine for inhibiting the development of and/or eliminating fungi in warm-blooded animal suffering from infections by these fungi.
8. A compound of formula (II)

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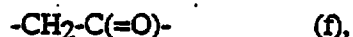
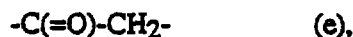


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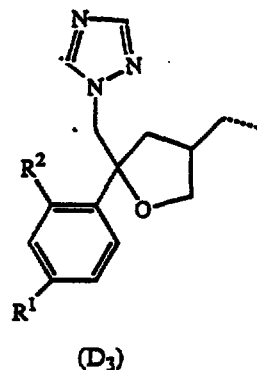
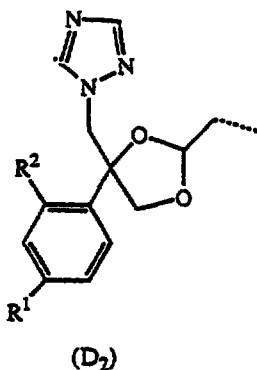
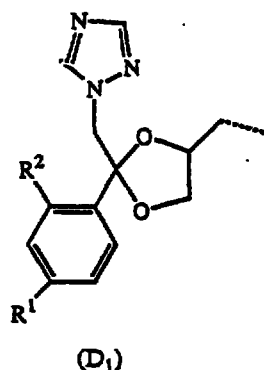
a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

A and B taken together form a bivalent radical of formula :



wherein one hydrogen atom in the radicals (a) and (b) may be replaced with a C₁₋₆-alkyl-radical and up to two hydrogen atoms in radical (c), (d), (e) or (f) may be replaced by a C₁₋₆ alkyl-radical;

D is a radical of formula



wherein

R¹ is halo; and

R² is hydrogen or halo.

9. A compound according to claim 8, wherein the compound is (±)-cis-4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-3,3-dimethylbutyl)-3H-1,2,4-triazol-3-one, a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof.

10. A process for preparing a compound as claimed in claim 1 characterized by

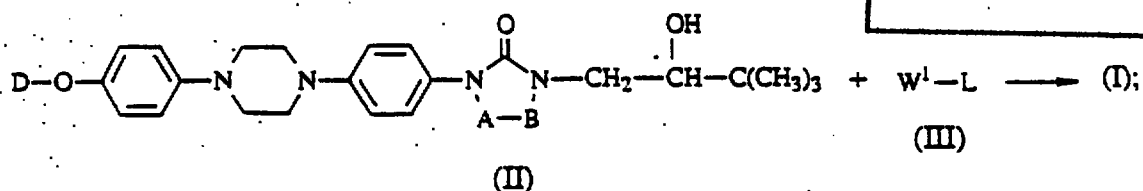
a) O-acylating or O-phosphorylating an intermediate of formula (II) wherein A, B and D are as defined in claim 1 with an acylating or phosphorylating reagent of formula (III),



REPLACEMENT SHEET

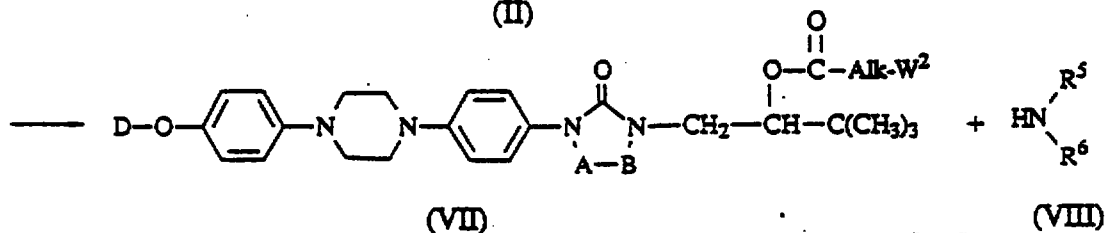
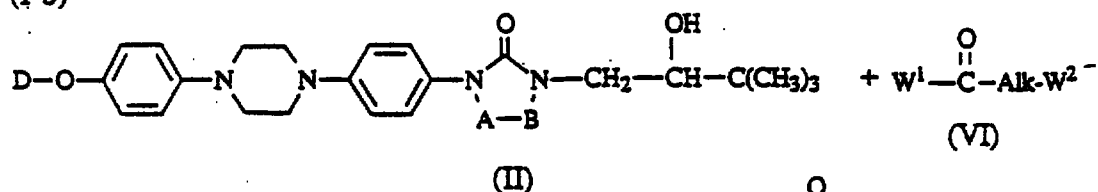
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wherein W^1 is a reactive leaving group such as hydroxy or halo, and L is as defined in claim 1; or

b) O -acylating an intermediate of formula (II) with reagent of formula (VI) wherein W^1 is a reactive leaving group such as hydroxy or halo, and W^2 is a reactive leaving group such as halo or a sulfonyloxy group, and subsequently reacting the thus obtained intermediate (VII) with an amine of formula (VIII), thus yielding a compound of formula (I-b)



— (I-b);

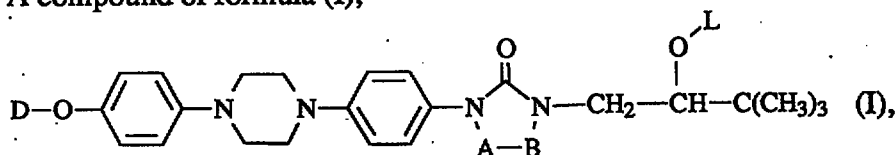
or converting the compounds of formula (I) into each other following art-known functional group transformation procedures; converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or base; or conversely, converting the salt form into the free base of the free acid by treatment with alkali, respectively an acid; and/or preparing stereochemically isomeric forms thereof.

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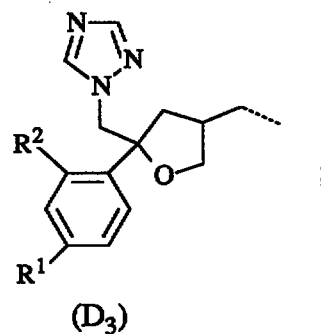
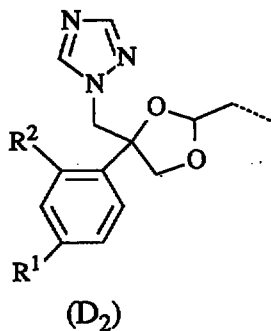
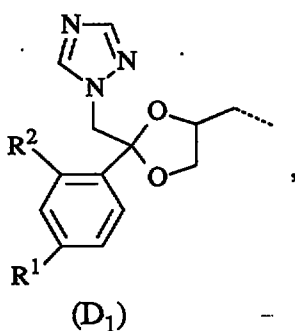
ABSTRACT

WATERSOLUBLE AZOLE ANTIFUNGALS

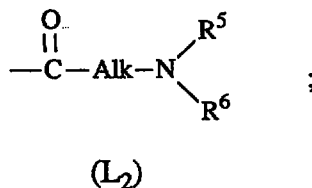
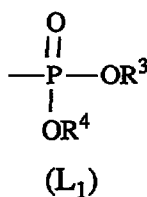
A compound of formula (I),



an acid or base addition salt thereof or a stereochemically isomeric form thereof, wherein A and B taken together form -N=CH-, -CH=N-, -CH₂-CH₂, CH=CH-, -C(=O)-CH₂-, -CH₂-C(=O); D is a radical of formula



L is a radical of formula



Alk is a C₁₋₄alkanediyl radical; R¹ is halo; R² is hydrogen or halo; R³ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁴ is hydrogen, C₁₋₆alkyl, phenyl or halophenyl; R⁵ is hydrogen or C₁₋₆alkyl; R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, or R⁵ and R⁶ taken together with the nitrogen atom to which they are attached form a heterocyclic ring. Active intermediates, compositions and methods of preparing compounds, compositions are described.