"~~ARALKYL~~ BENZYL ARALKYL ETHERS COMPOUNDS, ~~PROCESS FOR PREPARATION THEREOF, INTERMEDIATE COMPOUNDS,~~ USE OF SUCH COMPOUNDS, ~~METHODS OF TREATMENT AND/OR PREVENTION,~~ PHARMACEUTICAL COMPOSITION AND MEDICINE CONTAINING THE SAME~~"~~

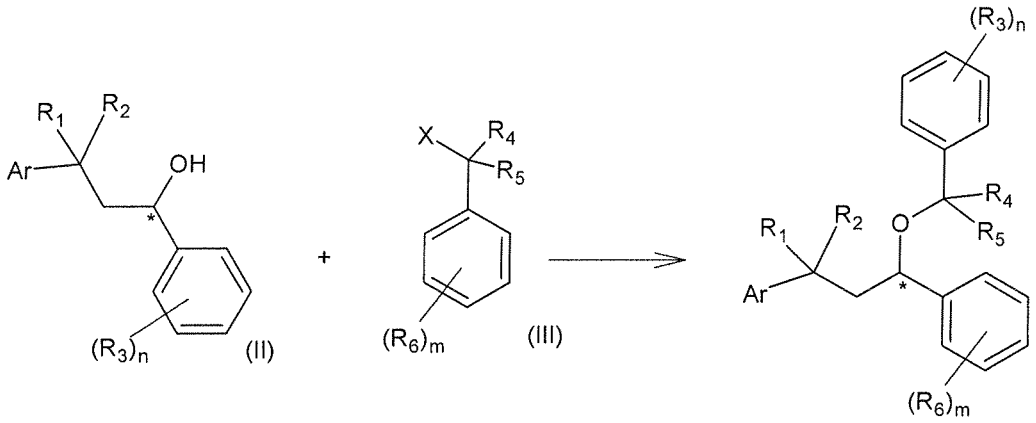
FIELD OF THE INVENTION

The present invention relates to compounds that are aralkyl benzyl ethers described in formula (I), their enantiomers, their diastereoisomers, their pro-drugs, esters, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and/or mixtures thereof in any proportions of these compounds and/or derivatives, to processes for the preparation of these compounds, intermediate compounds, pharmaceutical compositions comprising such compounds and/or derivatives, medicines including said compounds and/or derivatives, as well as to the uses of these compounds and/or derivatives in the treatment and/or prevention of conditions and/or diseases caused by microorganisms, such as fungi, bacteria and/or protozoa, for the inhibition of proliferation and/or survival of said microorganisms, for the treatment and/or prevention of colonization of microorganisms in an individual, and for the manufacture of a medicine.

The present invention also relates to the method of treatment and/or prevention of conditions in a mammal caused by fungi and/or other microorganisms such as bacteria and protozoa using aralkyl benzyl ethers compounds described in the formula (I) and, more particularly, compounds 1-[2-(2,4-dichlorophenyl)-2-{[4-(trifluoromethyl) benzyl] oxy} ethyl]-1H-imidazole and 1-[2-(2,4-dichlorophenyl)]-2-({4-[(2-phenyl)-2*H*-tetrazole] benzyl} oxy) ethyl]-1*H-imidazole.*

The present invention encompasses aralkyl benzyl ether compounds described in formula (I) and mixtures thereof in any proportions, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them. More particularly, the present invention relates to the use of aralkyl benzyl ether compounds described in formula (I) and, more particularly, the compounds 1-[2-(2,4-dichlorophenyl)-2-{[4-(trifluoromethyl) benzyl] oxy}

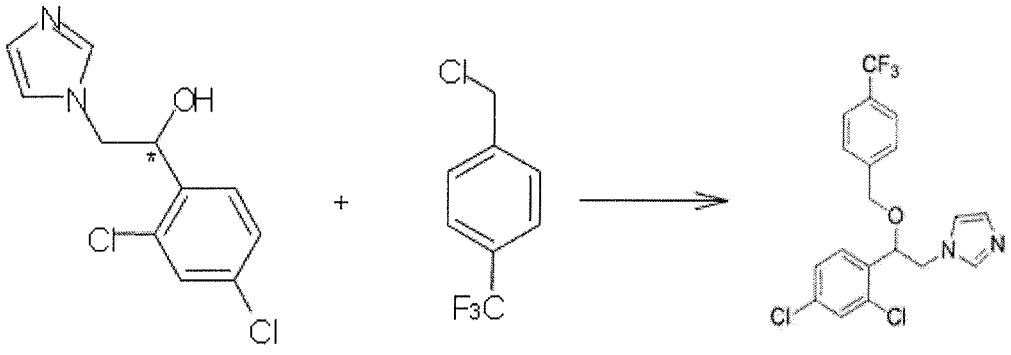
Said preparation process can be generally represented by the following procedure 1:

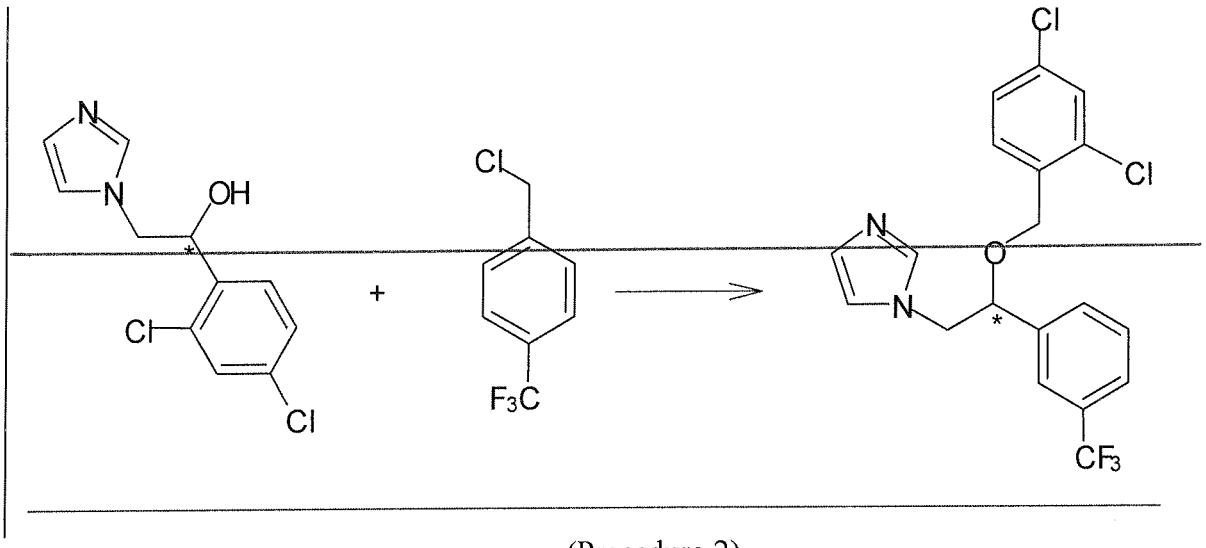


wherein Ar, R_1-R_6, *n* and *m* of formulas (II) and (III) are as defined in the detailed description of formula (I), and wherein **X** refers to elements selected from the group consisting of Cl, Br, I , MS (methanesulfonates) and TS (toluenesulfonates).

(Procedure 1)

Advantageously, the derivative 1-[2-(2,4-dichlorophenyl)-2-{[4-(trifluoromethyl)benzyl]oxy}ethyl]-1H-imidazole (BL-123), according to this invention can be prepared from 1-(2,4-dichlorophenyl)-2-(1*H-imidazole-1-yl)* ethanol and 1-(chloromethyl)-4-(trifluoromethyl)benzene according to the reaction below (Procedure 2).



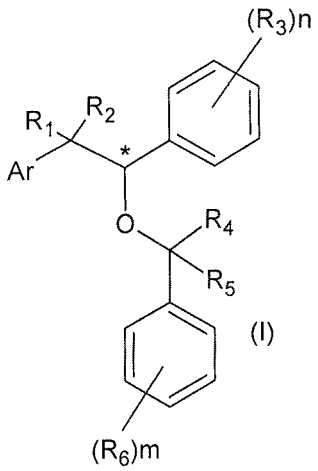


(Procedure 2)

The following examples illustrate, but do not limit to, procedures for the preparation of the compound 1-[2-(2,4-dichlorophenyl)-2-{[4-

CLAIMS

1. BENZYL ARALKYL ETHERS COMPOUNDS, CHARACTERIZED BY BEING OF FORMULA (I):



its salts, solvates, esters, enantiomers and/or pharmaceutically acceptable diastereoisomers, wherein:

Ar is imidazolyl;

$\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_4}$, and $\mathbf{R_5}$ are independently hydrogen, halogen or $C_{1\text{-}6}$ alkyl;

$\mathbf{R_3}$ is a substituent which is halogen, $C_{1\text{-}6}$ alkyl or **O-R'** where R' is hydrogen or lower alkyl;

$\mathbf{R_6}$ is trifluoromethyl or trichloromethyl;

n and ***m*** are independently an integer between 0 and 5;

with the proviso that when $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are hydrogen, $\mathbf{R_3}$ is halogen, **n** is an integer from 0 to 2, **m** is 1 and $\mathbf{R_6}$ is trifluoromethyl or trichloromethyl, anywhere in the benzyl ring.

2. COMPOUNDS as defined in claim 1, :

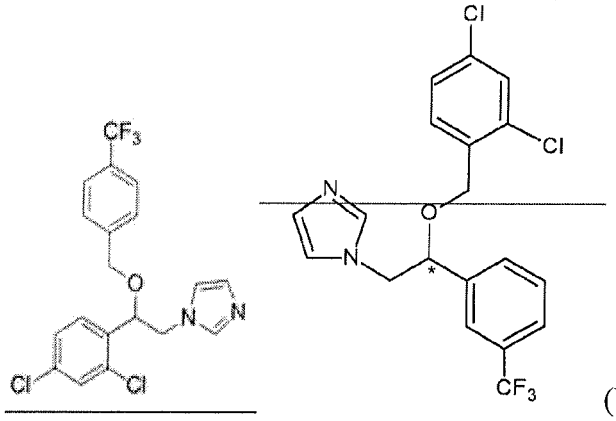
wherein said compounds have antifungal, antibacterial and/or antiparasite activity.

3. COMPOUNDS as defined in claim 1, wherein they are in the form of addition salts of pharmaceutically acceptable acids.

4. COMPOUNDS as defined in claims 1, wherein they are in the form of nitrate, chloride, bromhydrate, sulfate, bisulfate, phosphate, hydrogen phosphate, acetate,

benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, metasulfonate, benzenesulfonate and *p*-toluenesulfonate salts.

5. Compounds as defined in claims 1, wherein $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are hydrogen, $\mathbf{R_3}$ is chlorine, **n** is 2, **m** is 1, $\mathbf{R_6}$ trifluoromethyl, as defined by formula (V):



(V).

6. COMPOUNDS as defined in claim 5, wherein the compound is 1-[2-(2,4-dichlorophenyl)-2-{[4-(trifluoromethyl) benzyl] oxy} ethyl]-1H-imidazole, or their pharmaceutically acceptable salts.

7. USE of the compounds defined in any of claims 1 to 6 and/or mixtures thereof, for the preparation of a medicament for treatment and/or prevention of colonization by microorganisms in an individual.

8. USE, according to claim 7, wherein the microorganisms are fungi, bacteria or protozoa.

9. USE, according to claim 8, wherein the fungi are selected from the group consisting of the genera *Aspergilus, Microsporum, Epidermophyton, Trichophyton, Candida, Phycomyces, Zygomyces, Rhizopus, Mucor, Absidia, Malassezia, Exophiala, Piedraia, Trichosporum, Sporothrix, Cladosporium, Phialophora, Fosecaea, Histoplasma, Coccidioides, Fusarium, Penicillium, Blastomyces, Cryptococcus, Paracoccidioides, Scedosporium, Sacharomyces, Piedraia, Actinomyces, Keratinomyces, Nannizia, Arthroderma, Ctenomyces, Olpidium, Physodema, Synchytrium, Phytophora, Verticillium, Gliocladium, Rhytisma, Sclerotinia, Ophiostoma, Lophiodermium, Elsinoe, Capnodium, Mycosphaerella, Venturia, Gaeumannomyces, Alternaria, Bipolaris, Botrytis, Cercospora, Diplodia, Dreschlera,*

Exerohilum, Phoma, Phomopsis, Rhisoctonia, Puccinia, Erysphe, Phyllactinia, Uncinula, Phragmidium, Melampsora, Eutypha, Hypoxylon, Xylaria, Ceratobasidium, Heterobasidium, Thanatephorus and Armillaria.

10. USE, according to claim 8, wherein the fungi are dermatophytes.

11. USE, according to claim 10, wherein the dermatophyte fungi are selected from the group consisting of *Epidermophyton* sp, *Microsporum* sp and *Trycophyton* sp.

12. USE, according to claim 8, wherein the bacteria is selected from the group consisting of the genera *Actinomyces, Corynebacterium, Mycobacterium, Nocardia, Bacillus, Bifidobacterium, Clostridium, Erysipelothrix, Listeria, Staphylococcus, Streptococcus, Pneumococcus, Anaplasma, Ehrlichia, Neorickettsia, Wolbachia, Bacterioides, Bartonella, Bordetella, Borrelia, Brucella, Burkholderia, Campylobacter, Chlamydia, Chlamydophila, Escherichia, Klebsiella, Proteus, Salmonella, Serratia, Yersinia, Fusobacterium, Helicobacter, Acinetobacter, Mycoplasma, Ureaplasma, Neisseria, Meningococcus, Actinobacillus, Haemophilus, Pasteurella, Pseudomonas, Rickettsia and Treponema.*

13. USE, according to claim 8, wherein the protozoa is selected from the group consisting of the genera *Plasmodium, Toxoplasma, Balantidium, Coccidia, Cryptosporidium, Cylospora, Isospora, Sarcocystis, Babesia, Theileria, Dientamoeba, Giardia, Leishmania, Acanthamoeba, Blastocystis, Anaplasma, Ehrlichia, Trychomonas, Trypanosoma, Giardia and Entamoeba.*

14. USE of the compounds defined in any of claims 1 to 6, or mixtures thereof, for the manufacture of a medicament for the treatment and/or prevention of conditions and/or disease in an individual associated with microorganisms.

15. USE, according to claim 14, wherein the individual is a mammal.

16. USE, according to claims 15, wherein the mammal is a human.

17. USE, according to any of claims 14 to 15, wherein the micro-organisms are fungi, bacteria or protozoa.

18. USE, according to any of claims 14 to 16, wherein the conditions and/or diseases are selected from the group consisting of microsporic captis tinea, tinea

tonsuring, Kerion, tinea captis' athlete's foot, "broad bean" tinea, tinea barbae, tinea corporis, pedis tinea, tinea cruris, ear tinea, imbricate tinea, nail tinea, versicolored pityriasis, pityrosporum folliculitis, tinea nigra, black piedra, trichosporonosis, oral candidosis, vulvovaginal candidosis, balanopreputial candidosis, intertriginous candidosis, follicular candidosis, mucocutaneous candidosis, paracoccidioidomycosis, lobomycosis, chromomycosis, sporotrichosis, eumycetoma, histoplasmosis, phaeohyphomycosis, entomophthoromycosis, mucormycosis, cryptococcosis, coccidioidomycosis, north-american blastomycosis and/or Rhinosporidiosis.

19. USE, according to any of claims 14 to 16, wherein the conditions and/or diseases are selected from the group consisting of actinomycosis, Whiple disease, diphtheria, erythrasma leprosy, Buruli ulcer, paratuberculosis, tuberculosis, tuberculoma, pericarditis, erythema, mycetoma, anthrax, botulism, enterocolitis, enterotoxemia, gas gangrene, tetanus, erysipelas, meningitis, pneumonia, furunculosis, impetigo, endocarditis, rheumatoid fever, anaplasmosis, ehrlichiosis, angiomatosis, brucellosis, melioidosis, conjunctivitis, lymphogranuloma venereum, trachoma, psittacosis, dysentery, granuloma, typhoid fever, paratyphoid fever, gingivitis, legionellosis, leptospirosis, pleuropneumonia, gonorrhea, typhus, paints, syphilis, cancer, neurosyphilis, tularemia and cholera.

20. USE, according to any of claims 14 to 16, wherein the conditions and/or diseases are selected from the group consisting of malaria, toxoplasmosis, balantidiasis, coccidoidose, Cryptosporidiosis, cyclosporíase, isosporiasis, Sarcocystosis, babesiosis, dourine, theileriasis, trypanosomiasis, Dientamoebiasis, giardiasis, leishmaniasis, trichomoniasis, Chagas disease, amoebiasis and dysentery amoeboid.

21. PHARMACEUTICAL COMPOSITION, comprising as active ingredient at least one compound defined in any one of claims 1 to 6, and one or more pharmaceutically acceptable excipients.

22. PHARMACEUTICAL COMPOSITION, according to claim 21, wherein the said compound is ~~is~~:

1-[2-(2,4-dichlorophenyl)-2-{[4-(trifluoromethyl) benzyl] oxy} ethyl]-1H-imidazole or pharmaceutically acceptable salts thereof.

23. PHARMACEUTICAL COMPOSITION according to any of claims 21 and 22, wherein the composition is for topical, oral, parenteral or intraperitoneal administration.

24. PHARMACEUTICAL COMPOSITION according to any of claims 21 and 22, wherein the concentration of active ingredient varies in a range from 0.001 to 1000 mg.

25. MEDICINE, comprising as active ingredient at least one compound defined in any one of claims 1 to 6, and one or more pharmaceutically acceptable excipients.