PATENT SPECIFICATION

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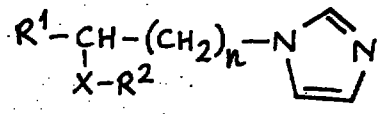


(54) 1-[2-(HALOPHENYLTHIO)-4-(p-CHLORO- OR -FLUOROPHENYL)-n-BUTYL] IMIDAZOLES

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 1 - [2 - (halophenylthio) - 4 - (p - chloro - or - fluorophenyl) - n - butyl] imidazoles and to processes for the preparation thereof. These compounds are useful as antifungal, antibacterial and antiprotozoal agents.

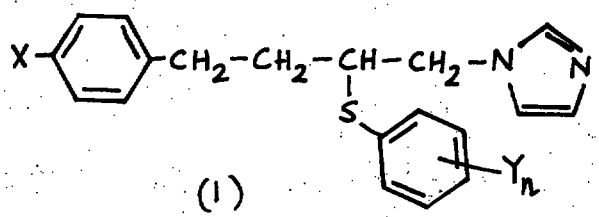
Our U.K. Patent No. 1,522,717 discloses certain substituted N-alkyl imidazole compounds represented by the following generic formula:



(A)

wherein R^1 and R^2 are each independently phenyl, phenyl straight chain lower alkyl, or phenyl straight chain lower alkenyl; or one of the above substituted in the phenyl ring with one or more substituents independently selected from alkyl groups of from one to four carbon atoms, halo and trifluoromethyl; X is oxygen or sulfur; n is an integer of from 1 to 8 with the proviso that n is not 1 when R^1 is phenyl or substituted phenyl; and the antimicrobial acid addition salts thereof. The class of compounds represented by the above formula plus salts thereof are described to exhibit antifugal, antibacterial and antiprotozoal activity.

Now it has been discovered that a group of compounds of the above class are particularly active. This group of compounds, as a highly active class different from that disclosed earlier and represented by Formula (A) above, is characterized by the following formula:

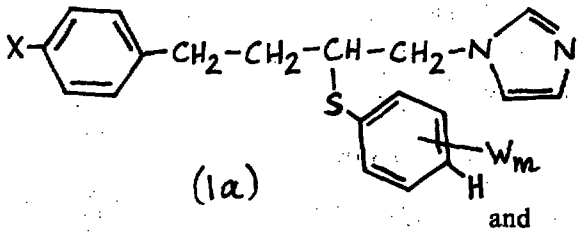


(I)

and the antimicrobial acid addition salts thereof wherein X is chloro or fluoro, each Y is bromo or chloro or fluoro, at least one Y being in the 2'-position, n is 1, 2, 3, 4 or 5 when Y is chloro, and n is 1 or 2 when Y is other than chloro.

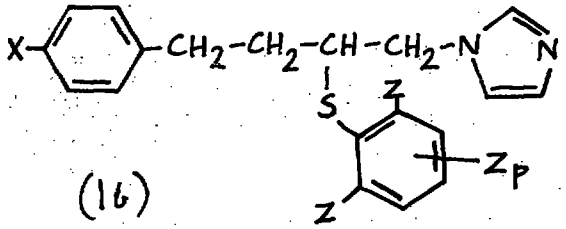
Preferred compounds of the invention are those of the formulae:

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(Ia)

and



(Ib)

and the antimicrobial acid addition salts thereof, wherein X is chloro or fluoro, each W is bromo or chloro or fluoro, at least one W being in the 2'-position, m is 1, 2, 3 or 4 when W is chloro, m is 1 or 2 when W is other than chloro, each Z is bromo or chloro or fluoro, p is 0, 1, 2 or 3 when Z is chloro, and p is 0 when Z is other than chloro.

Particularly preferred of the compounds of Formulas (I), (Ia) and (Ib), and the antimicrobial acid addition salts thereof, are those wherein n is 1, 2 or 3, or m is 1, 2 or 3, or p is 0 or 1 (Y or W or Z being chloro when n is 1, 2 or 3, m is 1, 2 or 3, or p is 1 and being other than chloro when n is 1 or 2, m is 1 or 2, or p is 0) and those wherein X is chloro, or when X is fluoro, then Y (or W or Z) is chloro. Further preferred are those wherein X and Y (or W or Z) are chloro. Particularly preferred of the latter are those wherein n is 2, m is 2 or p is 0 and those thereof wherein the two (Y or W or Z) chloro groups are in the 2',6'-positions of the phenyl ring. Thus, particularly preferred is the compound 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole, as well as the antimicrobial acid addition salts thereof.

The compounds of the present invention characterized by Formulas (I), (Ia) and (Ib) above, and the defined salts thereof, are distinguished by the discovery that certain specific molecular features provide a highly active class of compounds. These features are defined by 1) a 1,4-butylene chain linking the imidazole moiety and a p-chloro- or -fluoro-phenyl moiety, 2) a halophenylthio moiety attached to the C-2 carbon of the 1,4-butylene chain counting from the imidazole moiety and, most notably, 3) at least one halo being in the 2'-position of the phenyl ring in the halophenylthio moiety. This combination of features provides a surprisingly highly active, different class of compounds.

In a second aspect the present invention is concerned with a method of combatting fungi, bacteria and protozoa by administering a compound of the present invention or a composition containing same.

As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated. The term "halo" refers to bromo, chloro and fluoro. "Antimicrobial acid addition salts" of the subject bases refers to those salts which retain the antimicrobial properties of the free bases and which are neither biologically nor otherwise undesirable, formed with, for example, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; or inorganic acids such as acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid and salicyclic acid.

All compounds of Formula (I) possess at least one chiral center, i.e., the carbon atom to which are attached the S, H and two CH_2 moieties. Accordingly, the compounds of the present invention may be prepared in either optically active form, or as a racemic mixture. Unless otherwise specified, the compounds described herein are all in the racemic form. However, the scope of the subject invention herein is not to be considered limited to the racemic form, but to encompass the individual optical isomers of the subject compounds, and various mixtures thereof.

If desired, racemic intermediates or final products prepared herein may be resolved into their optical antipodes by conventional resolution means known *per se*, for example, by the separation (e.g., fractional crystallization) of the diastereomeric salts formed by reaction of, e.g., racemic compounds of Formula (I) with an optically active acid, or by the separation of the diastereomeric salts or esters formed by reaction of racemic compounds of Formula (II), infra, with an optically active acid. Exemplary of such optically active acids are the optically active forms of camphor-10-sulphonic acid, α-bromo-camphor-π-sulfonic acid, camphoric acid, menthoxy-acetic acid, tartaric acid, malic acid, diacetyltartaric acid and pyrrolidone-5-carboxylic acid. The separated pure diastereomeric salts or esters may then be cleaved by standard means to afford the respective optical isomers of the compounds of Formula (I) or (II).

The subject compounds of Formula (I) exhibit anti-fungal, anti-bacterial and anti-protozoal activity. For example, compounds of the present invention exhibit anti-fungal activity against human and animal pathogens such as

Microsporum audouini,
Microsporum gypseum,
Microsporum gypseum-canis,
Epidermophyton floccosum,
Trichophyton mentagrophytes,
Trichophyton rubrum,
Trichophyton tonsurans,
Candida albicans, and
Cryptococcus neoformans.

The compounds of the present invention also exhibit antifungal activity against the following fungi primarily of agricultural significance.

Aspergillus flavus,
Aspergillus niger,
Cladosporium herbarum,
Penicillium oxalicum,
Fusarium graminearum,
Penicillium spinulosum,
Penicillium notatum, and
Pithomyces chartarum.

In addition, the compounds of the present invention exhibit anti-bacterial activity against human and animal pathogens, such as

Staphylococcus aureus,
Streptococcus faecalis,
Corynebacterium acnes,
Erysipelothrix insidiosa,
Escherichia coli,
Proteus vulgaris,
Salmonella choleraesuis,
Pasteurella multocida, and
Pseudomonas aeruginosa.

Moreover, the compounds of the present invention exhibit anti-protozoal activity against protozoa such as *Trichomonas vaginalis* and *Trichomonas foetus.*

In general, the subject compounds of the instant invention exhibit a low level of toxicity. Moreover, these compounds demonstrate good solubility in the stratum corneum. Since dermatophyte (i.e., parasitic fungal) infections are usually localized in the dead tissue of the stratum corneum, solubility of anti-fungal agents in this tissue significantly enhances their effectiveness.

In view of the aforementioned activities, the subject compounds are found to be useful antimicrobials, having not only pharmaceutical but also agricultural and industrial application.

Accordingly, a further aspect of the present invention relates to compositions for pharmaceutical, agricultural, and industrial use, which compositions comprise the subject compounds of formula (I) in combination with a suitable carrier. A still further aspect of the present invention relates to methods of inhibiting a growth of

fungi, bacteria and protozoa by applying to a host object containing, or subject to attack by, fungi, bacteria or protozoa, an effective amount of a compound of the present invention or a suitable composition containing same.

In pharmaceutical applications, compositions may be solid, semi-solid or liquid in form such as tablets, capsules, powders, suppositories, liquid solutions, suspensions, creams, lotions and ointments. Pharmaceutically acceptable non-toxic carriers, or excipients normally employed for solid formulations include tricalcium phosphate, calcium carbonate, kaolin, bentonite, talcum, gelatin, lactose and starch; for semi-solid formulations there may be mentioned, for example, polyalkylene glycols, vaseline and other cream bases; for liquid formulations there may be mentioned, for example, water, oils of vegetable origin and low boiling solvents such as isopropanol, and hydrogenated naphthalenes. The pharmaceutical compositions containing the compounds of the present invention may be subjected to conventional pharmaceutical expedients such as sterilization and can contain conventional pharmaceutical excipients such as preservatives, stabilizing agents, emulsifying agents, salts for the adjustment of osmotic pressure and buffers. The compositions may also contain other therapeutically active materials. In pharmaceutical applications, the subject compounds and compositions may be administered to humans and animals by conventional methods, e.g., topically, orally and parenterally. Parenteral administration includes intramuscular as well as subcutaneous and intravenous administration. Intravenous injection of imidazole-type anti-fungals has been demonstrated to be effective in the treatment of systemic mycoses (see for example, Drugs, *9*, pp, 419—420, 1975, which describes the intravenous administration of miconazole, i.e. 1 - [2,4 - dichloro - β - 2',4' - dichlorobenzyloxy)phenethyl]imidazole nitrite, to patients with systemic candidiasis). Topical application is the preferred method of administration for pharmaceutical applications. For such treatment, an area having an existing fungal, bacterial or protozoal growth, or to be protected against attack by fungi, bacteria, or protozoa, may be treated with the subject compounds or compositions by, for example, dusting, sprinkling, spraying, rinsing, brushing, dipping, smearing, coating and impregnating. Topical pharmaceutical compositions containing the compounds of the present invention exhibit anti-fungal anti-baceterial and anti-protozoal activity over a wide range of concentration, for example, from about 0.1 to 10.0% by weight of the composition. In any event, the composition to be administered will contain a quantity of the subject compound in an amount effective for relief or prevention of the specific condition being treated.

The pharmaceutical compositions hereof typically comprise one or more subject compounds of Formula (I) and a pharmaceutically acceptable, non-toxic carrier, and are preferably formulated in unit dosage form to facilitate administration (unit dosage being the amount of active ingredient administered on one occasion).

In general, for systemic (e.g., oral or parenteral) administration it is expedient to administer the active ingredient in amounts between about 1 and 100 mg/kg body weight per day, preferably between about 5 and 50 mg./kg. body weight per day, preferably distributed over several applications (e.g. in 3 individual doses) in order to achieve most effective results. For localized (e.g. topical) administration, however, proportionately less of the active ingredient is required.

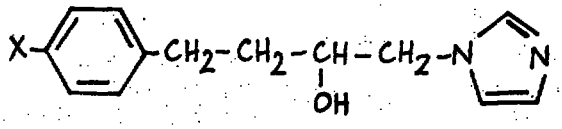
The exact regimen for pharmaceutical administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment, e.g., whether preventative or curative, the type of organism involved and, of course, the judgement of the attending practitioner.

In agricultural applications, the subject compounds may be applied directly to plants (e.g., seeds, foliage) or to soil. For example, compounds of the present invention may be applied to seeds alone or in admixture with a powdered solid carrier. Typical powdered carriers are the various mineral silicates, e.g., mica, talc, pyrophyllite, and clays. The subject compounds may also be applied to the seeds in admixture with a conventional surface-active wetting agent with or without additional solid carrier. Surface-active wetting agents that can be used are any of the conventional anionic, non-anionic or cationic types. As a soil treatment for fungi, the compounds of the invention can be applied as a dust in admixture with sand, soil or a powdered solid carrier such as a mineral silicate with or without additional surface-active agent, or the subject compounds can be applied as an aqueous spray optionally containing a surface-active dispersing agent and a powdered solid carrier. As a foliage treatment, the compounds of the invention

may be applied to growing plants as an aqueous spray which contains a surface-active dispersing agent with or without a powdered solid carrier and hydrocarbon solvents.

In industrial application, the compounds of the invention may be used to control bacteria and fungi by contacting the pathogens with the compounds in any known manner. Materials capable of supporting bacteria and fungi may be protected by contacting, mixing or impregnating these materials with the subject compounds. In order to increase their effect, the subject compounds may be combined with other pesticidal control agents such as fungicides, bactericides, insecticides, and miticides. A particularly important industrial/agricultural use for the compounds of the present invention is as a food preservative against bacteria and fungi which cause deterioration and spoilage of foods.

The compounds of Formula (I) may be prepared by forming a thioether from a suitable alcohol of Formula (II)

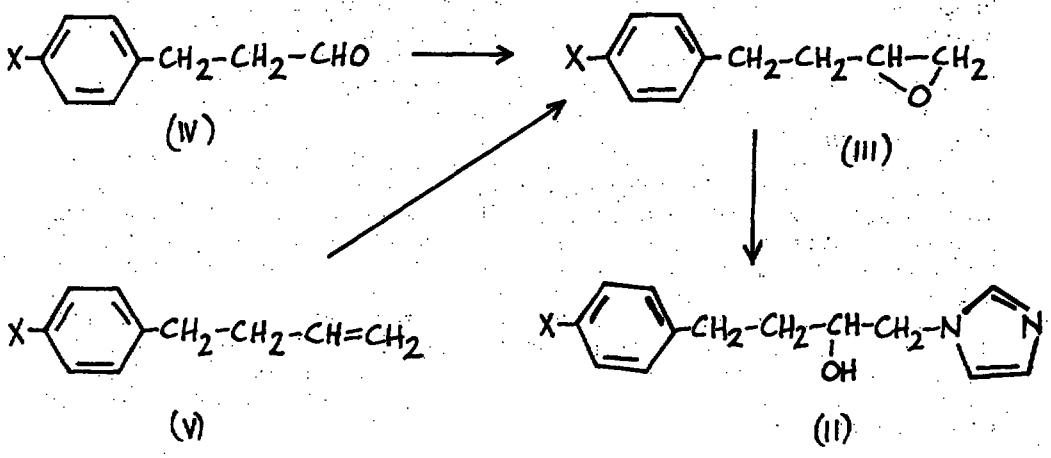


(II)

wherein X is as defined above. Compounds of Formula (II) may be prepared by a variety of reaction sequences.

For example, compounds of Formula (II) may be prepared by reaction Scheme A shown below.

Reaction Scheme A



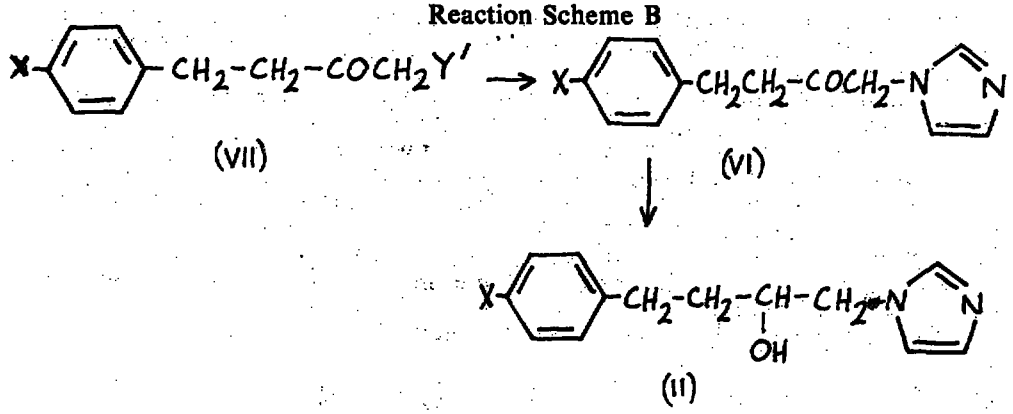
wherein X is as defined above.

In this reaction scheme the imidazole alcohol of Formula (II) is formed by opening of a terminal epoxide of Formula (III) with imidazole. This reaction is generally carried out using at least one mole and preferably an excess of imidazole relative to epoxide optionally in the presence of a salt (preferably an alkali metal salt) of imidazole. The reaction may either be carried out in the absence of solvent or, preferably, in an inert organic solvent, for example, a solvent such as dimethylformamide, hexamethylphosphoramide, acetonitrile, and the like. The temperature normally employed for such epoxide opening is in the range of from about −20 to about 100°C most preferably from about 20 to about 60°C.

Epoxides of Formula (III), insofar as they may not be known, may be prepared by a variety of well known methods, for example epoxidation of a terminal olefin (e.g., (V)) with, for example, a peracid, or by reaction of an aldehyde having one fewer carbon atom (e.g., (IV)) with the ylide prepared from trimethylsulfoxonium iodide or trimethylsulfonium iodide as described, for example, in *J. Am. Chem. Soc.*, *84*, p. 867 (1962); ibid, *87* p. 1353 (1965).

Another reaction scheme for preparing compounds of Formula (II) is shown in reaction Scheme B presented below

Reaction Scheme B



wherein X is as defined above and Y′ is chloro or bromo.

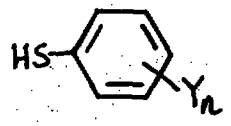
In this reaction scheme the hydroxy compound of Formula (II) is prepared by reduction of the corresponding ketone (VI), which in turn is prepared by reaction of an α-halo ketone (VII) with imidazole.

The α-halo ketones may be readily prepared by general methods known in the art, for example from the corresponding dihydrocinnamic acid by reaction of the acid chloride or bromide with diazomethane followed by treatment of the resulting diazoketone with HY′.

The α-halo ketone is contacted with imidazole in an inert organic solvent to afford the keto imidazole of Formula (VI). The reaction is carried out utilizing at least a molar amount and, preferably, an excess of imidazole relative to halo ketone. The reaction may be carried out in the absence of solvent or, preferably, in an inert organic solvent such as for example dimethylformamide, hexamethylphosphoramide and acetonitrile. The reaction is suitably carried out at a temperature initially between about −10 and 100°C most preferably between about 25°C and 80°C.

In the next step the keto imidazole of Formula (VI) is reduced to the hydroxy imidazole of Formula (II) utilizing a conventional metal hydride reducing agent such as, for example, sodium borohydride. The reaction is suitably carried out in an alcoholic solvent such as, for example, methanol or ethanol at a reduced temperature, for example, between about −10 and +25°C., most preferably about 0°C.

Compounds of Formula (I) may be prepared from the compounds of Formula (II) by a two-step sequence involving conversion of the hydroxy group to a suitable leaving group such as a halide (e.g., a chloride or bromide) or a sulfonate ester (e.g., methanesulfonate or p-toluenesulfonate) which is then reacted with the corresponding thiophenol



where Y and n are as defined above, preferably in the presence of base, e.g. potassium carbonate, or by using a metal salt thereof.

The conversion from the alcohol to the halide or sulfonate ester is carried out by means well known in the art. For example, the alcohol may be halogenated using a halogenating agent such as thionyl chloride or thiony bromide, either neat, or in an inert organic solvent such as dichloromethane or chloroform, at a temperature between about 0 and 80°C, preferably between about 20 and 80°C. The halogenation reaction may be carried out in the presence of molar equivalent of a base (e.g., pyridine) if desired. Alternate halogenation procedures include, for example, the use of triphenylphosphine with either carbon tetrachloride, carbon tetrabromide, or N-chloro (or N-bromo) succinimide. When utilising thionyl chloride or thionyl bromide without the use of added base, the hydrochloride or hydrobromide salt of the corresponding halo compound is produced. This salt may be neutralized (e.g. with potassium carbonate) prior to its use in the alkylation step, or the salt may be used directly if excess thiophenyl salt is utilized.

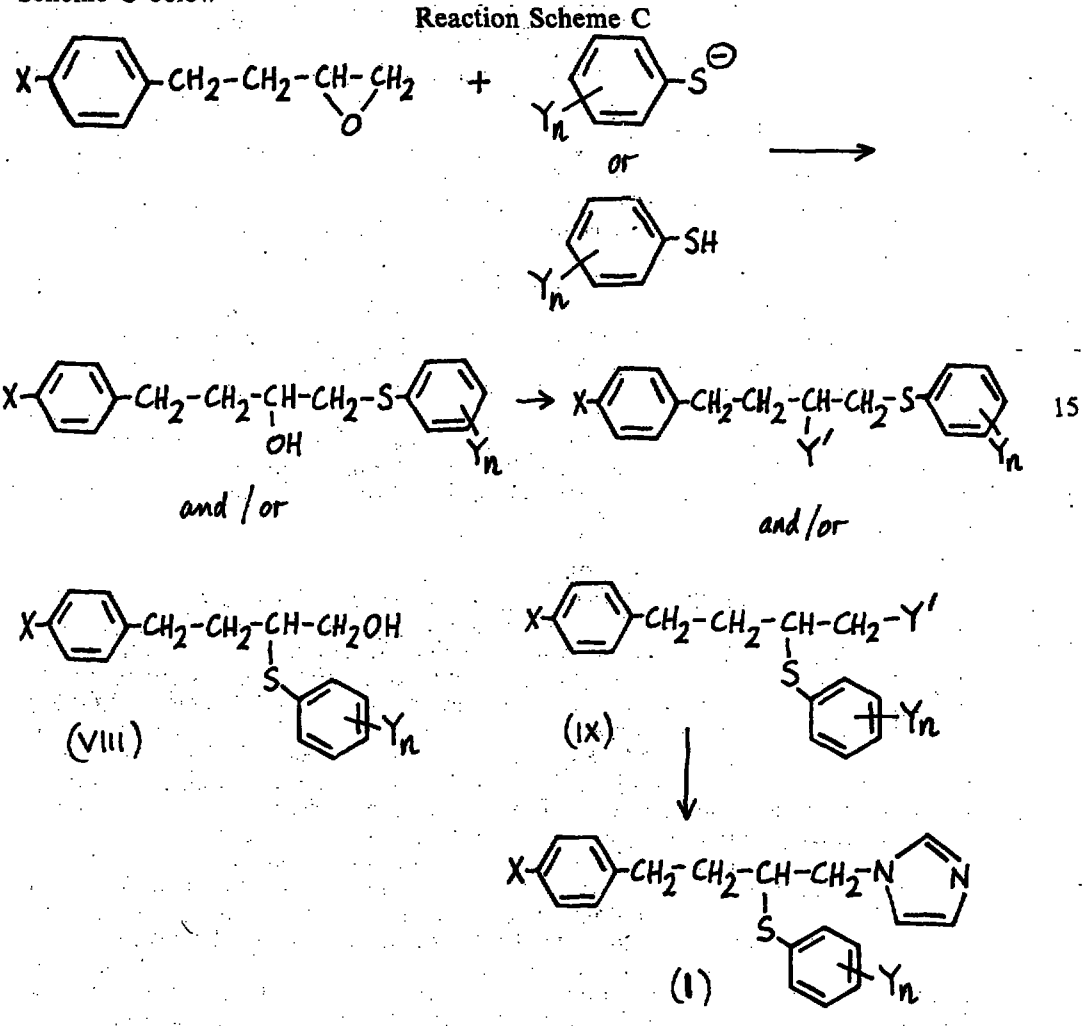
Sulfonate esters may be prepared by the standard procedure of treating the

alcohol with an excess of, for example, methanesulfonyl chloride or p-toluenesulfonyl chloride, in the presence of a base, for example pyridine or triethylamine. This reaction is carried out at a temperature from about −20 to +50°C, preferably between about 0 and 20°C.

The halide or sulfonate ester prepared as described above, is then treated with thiophenol preferably in the presence of base, or with a salt, preferably an alkali metal salt such as the sodium or potassium salt, of the corresponding thiophenol, in the presence of an inert organic solvent such as acetone or methanol, at a temperature of about 20 about 80°C. If desired, the metal salt of the thiophenol may be performed prior to addition of the halide.

Compounds of Formula (I) may also be prepared as depicted in reaction Scheme C below

Reaction Scheme C



wherein Y' is a leaving group and each of X, Y and n is as defined above.

In this scheme the epoxide of Formula (III) described earlier is opened with a thiophenol or a metal salt thereof, to afford the compound of Formula (VIII). This reaction is carried out utilizing, preferably, an alkali metal salt of the thiophenol, most preferably the sodium salt, in an inert organic solvent such as, for example, tetrahydrofuran or acetone at a temperature of between 0 and 67°C, or using the free thiophenol in the presence of an acid catalyst, e.g., perchloric acid, under similar conditions.

In the next step the hydroxy group of the compound of Formula (VIII) is converted to a leaving group such as a halide (e.g., chloro or bromo) or sulfonate ester (e.g., p-toluenesulfonate or methanesulfonate) by treatment with, e.g., a halogenating agent such as, for example, thionyl chloride, neat, or preferably in an inert solvent such as dichloromethane, or with, for example, p-toluenesulfonyl chloride, in a solvent such as pyridine. The product of Formula (IX) may exist in

either or both forms depicted, and may be interconvertible through an episulfonium intermediate.

In the final step, the compound of Formula (IX) is converted to the final product of Formula (I) by treatment with imidazole. This reaction is carried out in an inert organic solvent such as for example acetonitrile or dimethylformamide at a temperature of about 0 to about 100°C.

The thiophenol reagents can be prepared from the corresponding phenols by methods known generally in the art, for example, as described by M. S. Newman and H. A. Karnes, *J. Org. Chem.* 1973, Vol. 31, p. 3980.

The compounds of the invention can be isolated as free bases; however, since some of the compounds in base form are oils, it is more convenient to isolate and characterize the compounds as acid addition salts. These salts are prepared in the usual manner, i.e., by reaction of the base compound with a suitable inorganic or organic acid, described above. Salts formed with dibasic acids (e.g., oxalic acid) may contain one or two molecules of base per molecule of acid. All oxalates described herein contain one molecule of oxalic acid per molecule of imidazole base. If desired, the salts can be readily converted to the free base form by treatment with alkali, such as potassium carbonate, sodium carbonate or sodium or potassium hydroxide.

The following specific preparations and examples are illustrative of the present invention and should not be considered as limitative thereof in any manner.

Preparation 1

3 - (4 - Fluorophenyl) - 1 - propanol (34 g) in anhydrous methylene chloride (200 ml) was added directly to a well stirred suspension of pyridinium chlorochromate (71.5 g) in methylene chloride (400 ml). After two hours at room temperature, ether was added to precipitate the reagent, the reaction mixture decanted and the residue washed with ether. The combined organic extracts were filtered through Florisil (Trade Mark), evaporated and the product distilled under reduced pressure to give 3 - (4 - fluorophenyl)propionaldehyde as a colorless oil.

In a similar manner, 3 - (4 - chlorphenyl)propionaldehyde, an oil, was prepared.

Preparation 2

This preparation illustrates the process in reaction Scheme A.

3 - (4 - Fluorophenyl)propionaldehyde (20.6 g) was added under nitrogen to the ylide prepared from trimethylsulfonium iodide (31.8 g) and sodium hydride (55% dispersion in oil; 7.48 g) in dry dimethylsulfoxide (100 ml), according to the procedure in *Journal of the American Chemical Society*, Vol. 87, page 1353 (1965). After one hour at −10°, the solution was allowed to come to 0°, poured into 500 ml of ice water and the product extracted with ether (3×300 ml). The extract was washed well with water, dried ($MgSO_4$) and evaporated to give an oil, 1,2 - epoxy - 4 - (4 - fluorophenyl)butane, used directly in the next step.

The oil from above in a few ml of tetrahydrofuran was added to the mixture prepared by reacting imidazole (9.18 g) and sodium hydride (50% dispersion in mineral oil; 3.24 g) in 200 ml tetrahydrofuran until the evolution of hydrogen ceases. The mixture was heated under reflux overnight, evaporated to dryness and the residue extracted with a small volume of dichloromethane. This solution was filtered and chromatographed on silica gel eluting with 10% methanol in dichloromethane. Trituration with ethyl acetate/hexane gave 1 - [2 - hydroxy - 4 - (4 - fluorophenyl) - n - butyl]imidazole as colorless crystals, m.p. 120.5—122.5°C.

Similarly, preceding as above, substituting 3 - (4 - chlorophenyl)propionaldehyde for 3 - (4 - fluorophenyl)propionaldehyde, there is prepared 1 - [2 - hydroxy - 4 - (4 - chlorophenyl) - n - butyl]imidazole, m.p. 105—109°C.

Preparation 3

A solution of 6.0 g of 1 - [2 - hydroxy - 4 - (4 - chlorophenyl) - n - butyl]imidazole in 30 ml of thionyl chloride was warmed at 65—70°C for one hour. Evaporation to dryness afforded 1 - [2 - chloro - 4 - (4 - chlorophenyl) - n - butyl]imidazole hydrochloride.

Similarly 1 - [2 - chloro - 4 - (4 - fluorophenyl) - n - butyl)]imidazole hydrochloride is prepared.

The free base may be obtained for use in the subsequent alkylation steps, if desired, by shaking the hydrochloride in dichloromethane with excess aqueous

potassium carbonate solution, washing the organic layer with water, drying over magnesium sulfate and evaporating to dryness in vacuo to remove all traces of dichloromethane.

EXAMPLE 1

A mixture of 6.46 g of 1 - [2 - chloro - 4 - (4 - chlorophenyl) - n - butyl]imidazole, 8.5 g of 2,6 - dichlorothiophenol and 6.4 g of anhydrous potassium carbonate in 100 ml of acetone was stirred and refluxed for 18 hours. The solvent was evaporated under reduced pressure and 100 ml of water was added. The resulting mixture was extracted with 300 ml of ether and the ether extract washed twice with water and dried ($MgSO_4$) to afford a solution containing 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole.

The nitrate salt was precipitated by the dropwise addition of 70% nitric acid (d=1.42) to the etheral solution until precipitation was complete. The resulting salt was recrystallized from acetone-ethyl acetate as colorless blades, m.p. 162—163° (foaming).

In a similar manner, 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole nitrate salt, m.p. 131.5—132.5°C was prepared.

EXAMPLE 2

A mixture of 1,2-epoxy-4(4-chlorophenyl)butane (3.65 g), 2,6-dichlorothiophenol (4.0 g) and anhydrous potassium carbonate (200 mg) in acetone (60 ml) was stirred under reflux under nitrogen for about 4 hours. After removal of the solvent, ether (150 ml) was added and the extract washed with water, dried ($MgSO_4$) and evaporated.

The above material in 100 ml dichloromethane was treated with 6 ml of thionyl chloride, heated under gentle reflux for one hour, and the solution evaporated to dryness and evacuated to remove traces of thionyl chloride. The residue was treated with 7 g of imidazole and 30 ml of acetonitrile and stirred overnight at 55°C and for one day at 85°C. The solvent was evaporated and after the addition of 50 ml water the residue was extracted with ether. The ether extract was washed well with water and dried ($MgSO_4$) to afford a solution containing 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole, which was precipitated and purified as its nitrate salt, m.p. 162.5—164.5°C.

Similarly, 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]-imidazole - nitrate salt, m.p. 131.5—132.5°C, was prepared.

EXAMPLE 3

Following the procedures in Preparations 1, 2 and 3, and Examples 1 or 2 using equivalent amounts of the appropriate starting materials, there may be obtained the following compounds. Where indicated, the compounds may be further characterized by conversion to the indicated acid addition salt.

1 - [2 - (2,5 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 155.5—157°C.

1 - [2 - (2,3 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl] - imidazole - nitrate salt, m.p. 136—139.5°C.

1 - [2 - (2 - chlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 136—136.5°C.

1 - [2 - (2 - bromophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 137—138°C.

1 - [2 - (2,6 - dibromophenylthio) - 4 - (4 - chlorophenyl) - n - butyl] - imidazole.

1 - [2 - (2,4 - dibromophenyl) - 4 - (4 - chlorophenyl) - n - butyl]imidazole

1 - [2 - (2,4,6 - trichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole, m.p. 136—137°C; nitrate salt, m.p. 165—166°C.

1 - [2 - (2,5 - dichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 128.5—131°C.

1 - [2 - (2,3 - dichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole

1 - [2 - (2 - chlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 123—124°C.

1 - [2 - (2 - bromophenylthio) - 4 - (4 - fluorophenyl)butyl]imidazole

1 - [2 - (2,6 - dibromophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole

1 - [2 - (2,4 - dibromophenylthio) - 4 - (4 - fluorophenyl) - n - butyl] - imidazole
1 - [2 - (2,4,6 - trichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 163—164°C.
1 - [2 - (2,3,6 - trichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole - nitrate salt, m.p. 138—142°C (foaming).
1 - [2 - (2,3,4 - trichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,5 - trichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,4,5 - tetrachlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,5,6 - tetrachlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl)] - imidazole
1 - [2 - (2,3,5,6 - tetrachlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3 - dibromophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,5 - dibromophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,6 - difluorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,5 - difluorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,4 - difluorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2 - fluorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3 - difluorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,4 - trichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl] - imidazole
1 - [2 - (2,3,6 - trichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,5 - trichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,4,6 - tetrachlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,5,6 - tetrachlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3,4,5 - tetrachlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3 - dibromophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,5 - dibromophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2 - fluorphenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,3 - difluorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,4 - difluorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole
1 - [2 - (2,5 - difluorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole and
1 - [2 - (2,6 - difluorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole.

EXAMPLE 4

Nitric acid (70%; d=1.42) was added dropwise to a stirred solution of 2.0 g of 1 - [2 - (2 - chlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole in 30 ml of anhydrous ether until precipitation was complete. The product was filtered off, washed with ether, air dried, and recrystallized from ethyl acetate to yield 1 - [2 - (2 - chlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole nitrate, m.p. 136—136.5°C.

In similar manner, all compounds of Formula (I) in base form can be converted to their antimicrobial acid addition salts by treatment with the appropriate acid, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric aicd, acetic acid, propionic acid, glycolic acid, lactic acid,

pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid or salicylic acid.

EXAMPLE 5

1 - [2 - (2,6 - Dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole nitrate (2.0 g) in 100 ml of ether was stirred with excess dilute potassium carbonate solution until the salt was completely dissolved. The organic layer was then separated, washed twice with water, dried over magnesium sulfate and evaporated to yield 1 - [2 - (2,6 - dichlorophenylthio - 4 - (4 - chlorophenyl) - n - butyl]imidazole, m.p. 68—70.5°C (foaming) after crystallization from cyclohexane.

In similar manner, the antimicrobial acid addition salts of all compounds of Formula (I) can be converted to the corresponding compounds in base form.

EXAMPLE 6

The following illustrates the preparation of representative pharmaceutical formulations which may be used for controlling fungi, bacteria and protozoa, utilizing an active compound such as a salt of 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole.

A. Topical Formulation

	grams
Active compound	0.2—2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	qs 100

All of the above ingredients, except water, are combined and heated at 60°C, with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to provide 100 g of the cream formulation which is then cooled to room temperature.

B. IV Formulation

Active compound	0.5 g
Propylene glycol	20 g
Polyethylene glycol 400	20 g
Tween 80	1 g
0.9 Saline solution	qs 100 ml

The active compound is dissolved in propylene glycol, polyethylene glycol 400 and Tween 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 ml of the I.V. solution which is filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

"Tween" is a Registered Trade Mark.

C. Oral Formulation

	parts by weight
Active compound	200
Magnesium stearate	3
Starch	30
Lactose	116
PVP (polyvinylpyrrolidone)	3

The above ingredients are combined and granulated using methanol as the solvent. The formulation is then dried and formed into tablets (containing 200 mg of active compound) with an appropriate tabletting machine.

EXAMPLE 7

The antifungal activity of certain compounds of the present invention is illustrated by the following assay procedure:

A. Trichophyton mentagrophytes fungus culture for infection was grown on agar slants of Sabouraud dextrose for 4 weeks at room temperature. A 2% solution of corn starch was prepared by heating the starch in sterile distilled water. Approximately 7 ml of corn starch solution was added to each of 8 slants of culture. Suspension of organism was accomplished with vigorous pipetting and vortexing of the slants.

Guinea pigs (250—350 grams) were assigned to ten experimental groups of ten animals (5 female, 5 male). One day pre-challenge, all guinea pigs were clipped and shaved in the interscapular region, avoiding any abrasions or lacerations.

Animals were challenged by rubbing a toothbrush, which had been dipped in fungal suspension, over a 1.5 cm×1.5 cm shaved area. The rubbing continued until slight reddening occurred.

Treatment with test compound began 3 days postchallenge and was continued once daily for 5 consecutive days. At each treatment approximately 1 ml of formulation was applied to the infected area using a tongue depressor. Ten animals were not treated and served as untreated infection controls.

Hair was plucked from 10—20 sites in the infected area of each guinea pig. The hairs were innoculated onto plates containing Mycosel agar. One plate was used for each animal at each culture time (3, 7 and 14 days post-infection). Plates were incubated at room temperature (approximately 21°C) and read 7 days after innoculation.

Summary of Culture Results

Test Compound	Days Post Challenge 3*	4	7	14
Untreated controls	10/10**	10/10	10/10	8/10
0.5% Miconazole, in cream:	10/10	3/10	2/10	9/10
1-[2,4-dichloro-β-(2,4-dichlorobenzyl-oxy)phenethyl]-imidazole nitrate				
0.5% 1-[2-(2-chlorophenylthio)-4-(4-chlorophenyl)-n-butyl]-imidazole nitrate, in cream	10/10	0/10	0/10	0/10
Untreated controls	10/10	10/10	10/10	10/10
0.3% Miconazole, in cream	10/10	3/10	0/10	3/10
0.1% 1-[2-(2,5-dichlorophenylthio)-4-(4-chlorophenyl)-n-butyl]-imidazole nitrate, in cream	10/10	0/10	0/10	0/10
Untreated controls	10/10	10/10	10/10	10/10
0.3% Miconazole, in cream	10/10	3/10	0/10	3/10
0.1% 1-[2-(2-bromophenyl thio)-4-chlorophenyl)-n-butyl]imidazole nitrate, in cream	10/10	2/10	0/10	0/10

*Pretreatment culture
**Animals with positive culture/Total animals in group.

B. Swiss/Webster mice 17—20 gram, female, were given 0.25 mg of β-estradiol suspension, in a 0.2 ml volume, subcutaneously on Days 1, 3 and 5 to induce estrus. Estrus was then maintained with an injection of β-estradiol every 7 days.

A clinical isolate was obtained from human sputum. Organism to be injected is grown for 72 hours on Sabouraud Dextrose Agar (SDA) slants at 30°C. On the day of the challenge 2—3 ml of Sabouraud Dextrose Broth (SDB) was added to each slant of the organism and mixed by pipetting to achieve a homogenous suspension. Concentration of organisms for injection is approximately 10^{10} org/ml (2—3 ml of SDB is added to a culture of organism growing on SDA slant). 7 days after 1st estradiol injection approximately 25 μl of culture suspension is injected into each mouse vagina using a 20 gauge, 2 mm ball-tipped animal feeding needle.

The mice were initially treated 6 hours post-challenge and then twice daily, 6 hours apart, using a ball-tipped feeding needle for cream or liquid type formulations. The fluid type formulations were injected into the vagina until it overflowed. Treatments were carried out for 5 consecutive days. All animals received one treatment only on the fifth day so that they could be cultured during working hours, 6 hours post-treatment. The mice were cultured on Day 4 post-challenge (6 hours post-treatment) and Day 7 post-challenge (72 hours post-treatment). Cultures were obtained by vaginal washing using approximately 0.2 ml of sterile distilled water with an 18—20 gauge, 2 mm ball-tipped feeding needle. The wash was inoculated into a tube of SDB containing 100 μg oxytetracycline/ml. Cultures were incubated at 30°C for 48—72 hours then read microscopically. *Candida albicans* was confirmed by germ tube formation in 2—3 hours in sheep serum at 37°C.

Summary of Culture Results

Test Compound	6 Hours Post-Treatment % Negative	72 Hours Post-Treatment % Negative
Untreated	0	0
2% Econazole, in cream	10	0
1-[2,4-dichloro-β-(4-chlorobenzyloxy)phenethyl]-imidazole nitrate		
2% 1-[2-(2,4,6-trichlorophenylthio)-4-(4-fluorophenyl)-n-butyl]imidazole nitrate, in cream	80	56
Untreated	0	0
2% Micronazole, in cream	80	20
2% 1-[2-(2,6-dichlorophenylthio)-4-(4-chlorophenyl)-n-butyl]imidazole nitrate, in cream	100	100

EXAMPLE 8

Mouse Acute Oral Toxicity (LD_{50})

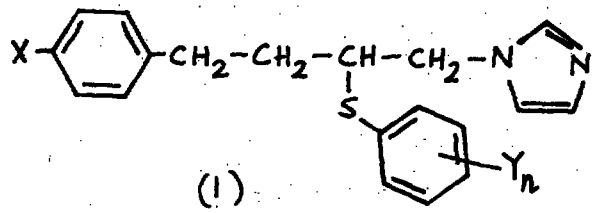
Protocol: The test material is suspended in a 0.5% low viscosity sodium carboxymethylcellulose vehicle. Concentrations are adjusted so that doses can be given in volumes of 0.1 ml/10 g body weight. Six groups (comprising 5 male and 5 female mice in each group) of mice are used. A single oral dose, per kilogram of body weight, of either 100 mg., 200 mg., 400 mg., 800 mg., 1600 mg. or 3200 mg. of 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole nitrate is administered to the mice. After administration, the mice are observed for a two-week period.

Using the above protocol, the acute oral LD_{50} of 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole nitrate is estimated to be >3200 mg/kg.

Three mice, given 3200 mg/kg, showed signs of toxicity. No signs of toxicity were seen for any of the other mice on this study.

WHAT WE CLAIM IS:—

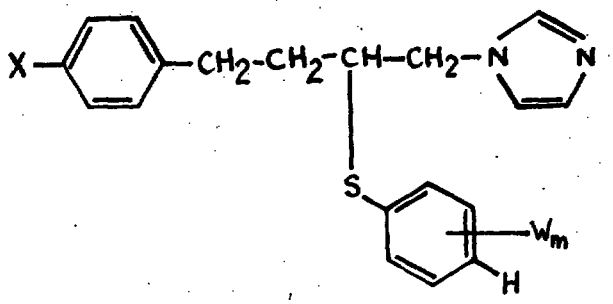
1. A compound of the formula:



(I)

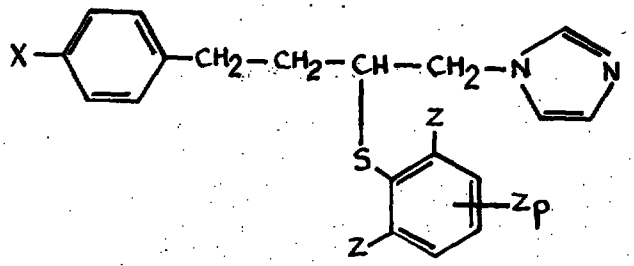
and the antimicrobial acid addition salts thereof, wherein X is chloro or fluoro, each Y is bromo or chloro or fluoro, at least one Y being in the 2'-position, n is 1, 2, 3, 4 or 5 when Y is chloro, and n is 1 or 2 when Y is other than chloro.

2. The compound of Claim 1 wherein n is 1, 2 or 3.
3. The compound of Claim 2 wherein X is chloro.
4. The compound of Claim 3 wherein Y is chloro.
5. The compound of Claim 2 wherein X is fluoro and Y is chloro.
6. The compound of Claim 4 wherein n is 2.
7. A compound of the formula:



and the antimicrobial acid addition salts thereof, wherein X is chloro or fluoro, each W is bromo or chloro or fluoro, at least one W being in the 2'-position, m is 1, 2, 3 or 4 when W is chloro, and m is 1 or 2 when W is other than chloro.

8. The compound of Claim 7 wherein m is 1, 2 or 3.
9. The compound of Claim 8 wherein X is chloro.
10. The compound of Claim 9 wherein W is chloro.
11. The compound of Claim 8 wherein X is fluoro and W is chloro.
12. The compound of Claim 10 wherein m is 2.
13. A compound of the formula:



and the antimicrobial acid addition salts thereof, wherein X is chloro or fluoro, each Z is bromo or chloro or fluoro, p is 0, 1, 2 or 3 when Z is chloro, and p is 0 when Z is other than chloro.

14. The compound of Claim 13 wherein p is 0 or 1.
15. The compound of Claim 14 wherein X is chloro.
16. The compound of Claim 15 wherein Z is chloro.
17. The compound of Claim 14 wherein X is fluoro and Z is chloro.
18. The compound of Claim 16 wherein p is 0.
19. The compound which is 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

* C L M S *

20. The compound which is 1 - [2 - (2,5 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

21. The compound which is 1 - [2 - (2 - chlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and antimicrobial acid addition salts thereof.

22. The compound which is 1 - [2 - (2,3 - dichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

23. The compound which is 1 - [2 - (2 - bromophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

24. The compound which is 1 - [2 - (2,6 - dichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

25. The compound which is 1 - [2 - (2,4,6 - trichlorophenylthio) - 4 - (4 - chlorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

26. The compound which is 1 - [2 - (2,5 - dichlorophenylthio) - 4 - (4 - fluorophenyl - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

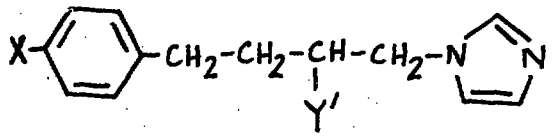
27. The compound which is 1 - [2 - (2,4,6 - trichlorophenylthio) - 4 - (4 - fluorophenyl) - n - butyl]imidazole and the antimicrobial acid addition salts thereof.

28. A composition useful for inhibiting the growth of fungi, bacteria or protozoa which comprises an effective amount of a compound of Claim 1 together with a suitable carrier therefor.

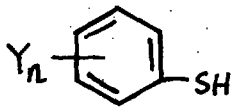
29. A method of inhibiting the growth of fungi, bacteria or protozoa which comprises applying to a host object containing, or subject to attack by, fungi, bacteria or protozoa an effective amount of a compound of Claim 1.

30. A process for the preparation of a compound as claimed in Claim 1 which comprises:

(a) converting a compound of the formula

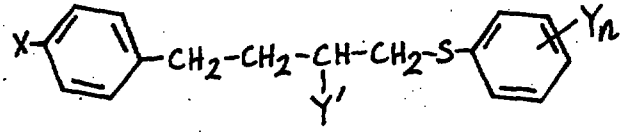


wherein X is as defined in Claim 1 and Y′ is a leaving group, or an acid addition salt thereof, to a thioether by reaction with

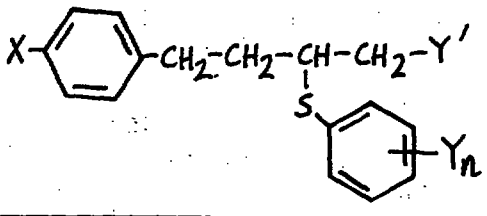


wherein Y and n are as defined in Claim 1, or with a salt thereof; or

(b) reacting a compound of the formula



and/or



wherein X, Y, and n are as defined in Claim 1 and Y' is a leaving group, with imidazole; or

(c) optionally converting a free base of Formula (I) to its acid addition salt; or

(d) optionally converting an acid addition salt to the corresponding free base of Formula (I).

31. A compound of Claim 1, substantially as exemplified herein.

32. A composition of Claim 28 substantially as exemplified herein.

33. A process for the preparation of a compound of Claim 1, substantially as described herein.

34. A compound of Claim 1 whenever prepared by a process according to Claim 30 or Claim 33.

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* C L M S *

ERRATA

SPECIFICATION No. 1,567,431

Page 1, line 20, *for* antifugal *read* antifungal
Page 2, line 42, *for* salicyclic *read* salicylic
Page 4, line 32, *for* anti-baceterial *read* anti-bacterial
Page 5, line 4, *for* application *read* applications
Page 6, line 35, *for* thiony *read* thionyl
Page 8, line 30, *for* (4-chlorphenyl) *read* (4-chlorophenyl)
Page 10, line 12, *for* (2,3,5,6- *read* (2,3,4,6-
Page 10, line 45, *for* (2-fluorphenylthio) *read* (2-fluorophenylthio)
Page 10, line 64, *for* aicd *read* acid
Page 13, line 16, *for* 0.2 ml *read* 0.1 ml
Page 13, line 34, *for* Micronazole *read* Miconazole

THE PATENT OFFICE
8th August, 1980