CONVENTION APPLICATION FOR A PATENT

(a) Insert full name(s) of applicants.

BAYER AKTIENGESELLSCHAFT

(b) Insert address(es) of applicant(s)

Leverkusen, Germany

(c) Insert title of invention.

"NEW COMPOUNDS, THEIR PRODUCTION AND THEIR MEDICINAL USE"

(d) Insert country in which first basic application was made.

Germany

(e) Insert date(s) of basic application(s).

in (d) Germany on (e) 25 November 1978 No. (f) P 28 51 116.2

(f) Insert number of basic application.

in (d) Germany on (e) No. (f)

in (d) Germany on (e) No. (f)

in (d) Germany on (e) No. (f)

in (d) Germany on (e) No. (f)

in (d) Germany on (e) No. (f)

(g) Insert date Form signed.

23rd day of November 1979

(h) Signature(s) of applicant(s).

(3) Insert date Form signed.

23rd day of November 1979

By Its Patent Attorneys,

ARTHUR S. CAVE & CO.

Patent and Trade Mark Attorneys,

1 Alfred Street, Sydney, New South Wales, Australia 2000.

Dated this (g) 23rd day of November 1979.

JAMES G. SIELY F. I. P. A. A.

AUSTRALIAN PATENT OFFICE

26 NOV 1979
AUSM "IA PATENT DECLARATION
FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA
Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER
PART XVI FOR A PATENT OR PATENT OF ADDITION

To be signed by the applicant(s) or in the case of a Company, to be
signed by a person authorised by the Company

In support of the Convention application made for a patent

(a) Insert title of Invention.

"NEW COMPOUNDS...THEIR PRODUCTION AND THEIR
MEDICINAL USE"

(b) Insert full name of declarant(s).

I/we (b) James Gordon Siely, Patent Attorney,

(c) Insert address of declarant(s).

of (c) 1 Alfred Street, Sydney, New South Wales,
Australia

do solemnly and sincerely declare as follows:

1. I am/we are the applicant(s) for the patent

(OR, IN THE CASE OF AN APPLICATION BY A BODY CORPORATE.)

1. I am/we are authorised by BAYER AKTIENGESELLSCHAFT

the applicant for the patent

(patent of addition) to make this declaration

on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following
country(ies) on the following date(s) namely:

in (d) Germany on (e) 25 November 1978 No. (f) P 28 51 116.2
by (g) Bayer Aktiengesellschaft

in (d) on (e) No. (f)
by (g)

in (d) on (e) No. (f)
by (g)

3. I am/we are the actual inventor(s) of the invention referred to in the basic application.

(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)

3. (g) 1) Erik Regel 2) Karl Heinz Bächel

3) Ingo Haller 4) Manfred Flempel

of (i) 1) Bergerheide 72a, D 5600 Wuppertal 1, Germany;
2) Bergerheide 62, D 5600 Wuppertal 1, Germany;
3) Viktoriastasse 99, D 5600 Wuppertal 1, Germany;
4) Pahlkestrasse 5, D 5600 Wuppertal 1, Germany;

is/are the actual inventor(s) of the invention and the facts upon which
the Company is entitled to make the application are as follows:

BAYER AKTIENGESELLSCHAFT is the assignee of
the said invention from the said inventors.

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first
application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at SYDNEY this 1st day of February, 1980.

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

A.S.C. - 4
Compounds which are hydroxyethyl-azoles of the general formula

\[
\begin{align*}
&\text{OH} \\
&C - \text{CH}_2 - \text{Az} \\
&\text{R} \\
&\text{R}^1 \\
&\text{R}^2 \\
&\text{R}^3 \quad \text{and} \\
&\text{n} \\
\end{align*}
\]

or a salt thereof

in which

Az represents imidazole or triazole,
R represents optionally substituted phenyl, naphthyl or tetrahydronaphthyl,
R\(^1\) represents optionally substituted phenyl or cycloalkyl and
R\(^2\) represents hydrogen, or
R\(^1\) and R\(^2\) together, in the o-position relative to one another, represent an optionally substituted methylene bridge with several members, or, together with the phenyl ring, represent naphthyl,
R\(^3\) represents halogen, alkyl, alkoxy or halogeno-alkyl and
n represents 0, 1, 2 or 3.
TO BE COMPLETED BY APPLICANT

Name of Applicant: BAYER AKTIENGESELLSCHAFT

Address of Applicant: Leverkusen, Germany.

Actual Inventor: Erik Regel
               Karl Heinz Büchel
               Ingo Haller
               Manfred Plempel

Address for Service: ARTHUR S. CAVE & CO., 1 Alfred Street, Sydney, New South Wales, Australia.

Complete Specification for the invention entitled

"NEW COMPOUNDS, THEIR PRODUCTION AND THEIR MEDICINAL USE"

The following statement is a full description of this invention, including the best method of performing it known to me:-
The present invention relates to certain new hydroxyethylazole compounds and to processes for their production and to their use as antimycotic agents.

It has already been disclosed that 1-(β-aryl)-ethylimidazole derivatives, such as, in particular, 1-[2,4-dichloro-β-(2,4-dichlorobenzyloxy)-phenethyl]-imidazole nitrate, have a good antimycotic action (compare DE-AS (German Published Specification) 1,940,388). However, their in vivo action is not always satisfactory, especially against Candida.

According to the present invention we provide compounds which are hydroxyethyl-azoles of the general formula

\[ \text{R}^1 \text{R}^2 \text{R}^3 \text{C} - \text{CH}_2 - \text{Az} \quad (\text{I}) \]

in which

- \text{Az} denotes an imidazole or triazole radical,
- \text{R} denotes an optionally substituted phenyl, naphthyl or tetrahydro-naphthyl radical,
- \text{R}^1 denotes an optionally substituted phenyl or cycloalkyl radical and
- \text{R}^2 denotes a hydrogen atom and, or
- \text{R}^1 and \text{R}^2 together, in the o-position relative to one another, denote an optionally substituted methylene bridge with several members, or, together with the phenyl ring, complete a naphthyl radical
- \text{R}^3 denotes a halogen atom or an alkyl, alkoxy or halogeno-alkyl group and
- \text{n} is 0, 1, 2 or 3.

The compounds of the present invention have powerful antimycotic properties.

According to the present invention we further provide a process for the production of compounds of the present
invention in which a) an azolylmethyl phenyl ketone of the general formula

\[ R^1 \text{O} \quad \text{C} \quad \text{CH}_2 \text{Az} \]  

(II)

in which

Az, R\(^1\), R\(^2\), R\(^3\) and \(n\) have the meaning indicated above,

is reacted with a Grignard compound of the general formula

\[ \text{R} - \text{Mg} - \text{X} \]  

(III)

in which

R has the meaning indicated above and

X denotes a halogen atom, preferably a chlorine or bromine atom,

in the presence of a diluent, or

b) a 1-halogeno-ethan-2-ol of the general formula

\[ \text{R}^1 \text{OH} \quad \text{C} \quad \text{CH}_2 \text{Y} \]  

(IV)

in which

R, R\(^1\), R\(^2\), R\(^3\) and \(n\) have the meaning indicated above and

Y denotes a halogen atom, preferably a chlorine or bromine atom,

is reacted with an azole of the general formula

\[ \text{Z} - \text{Az} \]  

(V)

in which

Az has the meaning indicated above and

Z denotes a hydrogen atom, or an alkali metal,

preferably in the presence of an acid-binding agent and preferably in the presence of a diluent; and the product of reaction variant (a) or (b) is, if desired, converted into a salt by reaction with an acid.
The hydroxyethylazoles of the formula (I) obtainable according to the invention can also be converted into salts by reaction with acids. Among the new hydroxyethylazole salts of the invention, those salts that are pharmaceutically acceptably are particularly important and are preferred.

Surprisingly, the hydroxyethyl-azoles according to the invention exhibit, in addition to a good antimycotic in vitro activity, a better, therapeutically usable in vivo activity against Candida than 1-[2,4-dichloro-β-(2,4-di-chlorobenzyloxy)-phenethyl]-imidazole nitrate, which is known and is recognised as a good agent of the same type of action. The active compounds according to the invention thus represent a valuable advance in pharmacy. Preferments follow.

Preferred hydroxyethyl-azoles of the present invention are those in which 

\[ \text{Az denotes an imidazol-1-yl, 1,2,4-triazol-1-yl or 1,3,4-triazol-1-yl radical, } \]

\[ \text{R denotes an optionally substituted phenyl, naphthyl or tetrahydronaphthyl radical, } \]

preferred substituents which may be mentioned being: halogen, preferably fluorine, chlorine and bromine, straight-chain or branched alkyl and alkoxy with in each case 1 to 4 carbon atoms, and halogenalkyl with 1 to 4 carbon atoms and up to 5 halogen atoms, preferably with 1 or 2 carbon atoms and up to 3 identical or different halogen atoms, halogens being, preferably fluorine and chlorine, and trifluoromethyl being mentioned as an example; \( R^1 \) denotes an optionally substituted phenyl or \( C_3 \) to \( C_7 \) cycloalkyl radical, preferred substituents which may be mentioned being: halogen, preferably fluorine, chlorine or bromine, and alkyl with 1 to 4, preferably with 1 to 5, carbon atoms and \( R^2 \) denotes a hydrogen atom, or \( R^1 \) and \( R^2 \) together, in the ortho-position relative to one another, denote a methylene bridge which has 3 to 5 methylene groups and is optionally monosubstituted or polysubstituted, preferred substituents which may be mentioned being: halogen, preferably fluorine, chlorine or bromine, and alkyl with 1 to 4, preferably with 1 to 2, carbon atoms, or \( R^1 \) and \( R^2 \) together with the phenyl ring, complete a naphthyl radical; \( R^3 \) denotes a halogen atom, preferably fluorine, chlorine or bromine, a straight-chain or branched alkyl or alkoxy group with in each case 1 to 4 carbon atoms, or a halogenoalkyl group with 1 to 4
atoms and up to 5 halogen atoms, preferably with 1 or 2
carbon atoms, and up to 3 identical or different halogen
atoms, halogens being, preferably, fluorine and chlorine
and trifluoromethyl being mentioned as an example; and
_n_ is 0, 1 or 2.

Very particularly preferred compound of the present
invention are those in which _Az_ denotes a imidazol-1-yl or
1,2,4-triazol-1-yl radical, _R_ denotes a phenyl radical,
which is optionally monosubstituted or disubstituted by
chlorine, fluorine or methyl, or denotes a naphthyl or
tetrahydronaphthyl radical; _R_ denotes a phenyl, cyclopentyl
or cyclohexy radical, which is optionally monosubstituted
or disubstituted by chlorine, bromine, fluorine or methyl,
and _R_ denotes a hydrogen atom, or _R_ and _R_ together,
in the ortho-position relative to one another, denote a
trimethylene, tetramethylene or pentamethylene bridge, which
is optionally substituted by chlorine or methyl, or, together
with the phenyl ring, complete a naphthyl radical; _R_ denotes
a chlorine or fluorine atom or a methyl group; and _n_ is
0 or 1.

The following compounds of the general formula (I)
may be mentioned specifically, in addition to the compounds
mentioned in the preparation examples:

![Chemical Structure](image)

<table>
<thead>
<tr>
<th><em>R</em></th>
<th><em>R</em></th>
<th><em>R</em></th>
<th><em>R</em></th>
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<tr>
<td>R</td>
<td>R'</td>
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<tr>
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<td>4-O</td>
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<td>4-O</td>
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<td>Cl-Cl</td>
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<tr>
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<td>3,4-(CH₂)₃-</td>
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<td>CH(N)</td>
</tr>
<tr>
<td>Cl</td>
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<td>CH(N)</td>
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<tr>
<td>Cl</td>
<td>3,4-(CH₂)₃-</td>
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<td>CH(N)</td>
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<tr>
<td>Cl</td>
<td>3,4-(CH₂)₃-</td>
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<td>Cl</td>
<td>3,4-(CH₂)₃-</td>
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<td>CH(N)</td>
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<tr>
<td>Cl</td>
<td>3,4-(CH₂)₃-</td>
<td>-</td>
<td>-</td>
<td>CH(N)</td>
</tr>
</tbody>
</table>
If, for example, 4-biphenyl imidazol-1-yl-methyl ketone and 4-chlorophenyl-magnesium chloride are used as starting materials, the course of the reaction can be represented by the following equation (process variant a):

\[
\begin{align*}
\text{C}_1-\text{H}_2-\text{Cl} & \quad \text{Cl}\text{-Mg-Cl} \\
\end{align*}
\]

If 1-(4-biphenyl)-1-(2,4-dichlorophenyl)-2-chloro-ethanol and sodium imidazole are used as starting materials, the course of the reaction can be represented by the following equation (process variant b):
Preferred compounds of formula (II) to be used as starting materials for process variant (a) are those in which R1, R2, R3 and n have the meaning indicated for the mentioned preferred and very particularly preferred hydroxyethyl-azoles of the invention.

The azolymethyl phenyl ketones of the formula (II) are novel. They can be prepared by reacting corresponding phenacyl halides of the formula

\[ R^1 \text{C} - \text{CH}_2 - \text{Hal} \]

in which

R1, R2, R3 and n have the meaning indicated above and Hal denotes a chlorine or bromine atom, with azoles in the presence of a diluent, such as, for example, dimethylformamide, and in the presence of an acid-binding agent, such as, in particular, an excess of azole, at temperatures between 20 and 80°C (in this context, compare also the statements in U.S. Patent Specification 3,658,813).

Examples of the starting substances of the formula (II) which may be mentioned are: 4-biphenyl imidazol-1-yl-methyl ketone, 4-((4'-chlorophenyl)yl) imidazol-1-yl-methyl ketone, 2-biphenyl imidazol-1-yl-methyl ketone, 4-(2',4'-dichlorobiphenyl)yl) imidazol-1-yl-methyl ketone, 2-chloro-4-biphenyl imidazol-1-yl-methyl ketone, 2-chloro-
4-(4'-chlorobiphenyl) imidazol-1-yl-methyl ketone, 4-cyclohexylphenyl imidazol-1-yl-methyl ketone, 4-cyclopentylphenyl imidazol-1-yl-methyl ketone, 4-chloro-3-cyclohexylphenyl imidazol-1-yl-methyl ketone, 4-(3-bromocyclohexyl)phenyl imidazol-1-yl-methyl ketone, 4-cyclopentyl-2-chlorophenyl imidazol-1-yl-methyl ketone, 4-cyclopentyl-2-fluorophenyl imidazol-1-yl-methyl ketone, 4-cyclopentyl-2-methylphenyl imidazol-1-yl-methyl ketone, 4-(1-methylcyclohexyl)phenyl imidazol-1-yl-methyl ketone, 4-cycloheptylphenyl imidazol-1-yl-methyl ketone, 4-cycloheptyl-2-chlorophenyl imidazol-1-yl-methyl ketone, 1,2,3,4-tetrahydro-naphth-6-yl imidazol-1-yl-methyl ketone, and indan-4-yl imidazol-1-yl-methyl ketone, and the corresponding 1,2,4-triazol-1-yl ketones and 1,3,4-triazol-1-yl ketones.

Preferred Grignard compounds of formula (III) to be used as starting materials for process variant (a) are those in which R has the meaning indicated for the mentioned preferred and very particularly preferred hydroxyethyl-azoles of the invention.

The Grignard compounds of the formula (III) are generally known compounds of organic chemistry. Examples which may be mentioned are: phenyl-magnesium chloride, 4-chlorophenyl-magnesium chloride, 2,4-dichlorophenyl-magnesium chloride, 2,6-dichlorophenyl-magnesium chloride, 2-chloro-6-fluorophenyl-magnesium chloride, 2-chlorophenyl-magnesium chloride, 3-chlorophenyl-magnesium chloride, 3,4-dichlorophenyl-magnesium chloride, naphth-2-yl-magnesium chloride and 1,2,3,4-tetrahydro-naphth-6-yl-magnesium chloride, and the corresponding bromides.

Preferred 1-halogeno-ethan-2-ols to be used as starting materials for process variant (b) are those in which R, R1, R2, R3 and n have the meanings indicated for the mentioned preferred and very particularly preferred hydroxyethyl-azoles of the invention.
The 1-halogeno-2-ols of the formula (IV) are novel. They can be prepared by reacting ketones of the formula (VI) with Grignard compounds of the formula (III) according to process variant (a) (in this context, compare also the statements in DE-OS (German Published Specification) 2,623,129 and the preparation examples).

Preferred azoles of formula (V) to be used as starting materials for process variant (b) are those in which Az has the meaning indicated for the mentioned preferred and very particularly preferred hydroxyethyl-azoles of the invention, and Z preferably denotes a hydrogen atom or sodium or potassium.

The azoles of the formula (V) are generally known compounds of organic chemistry.

All the solvents customary for a Grignard reaction can be used as the diluent for the reaction, according to the invention, in process variant (a). Preferred solvents include ethers, such as diethyl ether or tetrahydrofurane, and mixtures with other organic solvents, such as, for example, benzene.

The reaction temperatures can be varied within a substantial range in process variant (a). The reaction is preferably carried out between 20 and 120°C, more preferably between 30 and 80°C.

An excess of the Grignard compound of the formula (III) of 3 to 5 mols is preferably used per 1 mol of the compound of the formula (II) in carrying out process (a). Isolation of the compounds of the formula (I) is effected in known manner.

Preferred possible diluents for the reaction, according to the inventor, in process variant (b) are inert organic solvents. Preferred solvents include ketones, such as diethyl ketone, and in particular acetone and methyl ethyl ketone; nitriles, such as propionitrile, and in particular acetonitrile; alcohols, such as ethanol or isopropanol; ethers, such as tetrahydrofurane or dioxane; aromatic hydrocarbons; such as benzene, toluene and dichlorobenzene; formamides, such as, in particular, dimethylformamide, and
halogenated hydrocarbons, such as methylene chloride, carbon tetrachloride or chloroform.

If process variant (b) according to the invention is carried out in the presence of an acid-binding agent, it is possible to add any of the inorganic or organic acid-binding agents which can usually be employed, such as alkali metal carbonates, for example sodium carbonate, potassium carbonate and sodium bicarbonate, or such as lower tertiary alkylamines, cycloalkylamines or aralkylamines, for example triethylamine, N,N-dimethylcyclohexylamine, dicyclohexylmethylamine or N,N-dimethylbenzylamine, and furthermore pyridine and diazabicyclooctane. An excess of azole is preferably used.

The reaction temperatures can be varied within a substantial range in process variant (b). The reaction is preferably carried out between 30 and 200°C at the boiling point of the solvent.

1 to 2.5 mols of azole and 1 to 2.5 mols of acid-binding agent are preferably employed per 1 mol of the compounds of the formula (IV) in carrying out process variant (b) according to the invention. If an alkali metal salt is used, 1 to 1.5 mols thereof are preferably employed per 1 mol of the compound of the formula (IV). To isolate the compounds of the formula (I), the solvent is distilled off and the residue is washed with water directly or after being taken up in an organic solvent, in which case the organic phase is dried over sodium sulphate and freed from solvent in vacuo. The residue is appropriately purified by distillation or recrystallisation or by chromatography.

All the acids which give rise to physiologically acceptable salts can be used for such salt preparation. These acids include, preferably, hydrogen halide acids, such as for example, hydrochloric acid and hydrobromic acid, in particular hydrochloric acid, and furthermore phosphoric acid, nitric acid, sulphuric acid, monofunctional and bifunctional carboxylic acids and hydroxycarboxylic acids, such as, for example, acetic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid, salicylic acid, sorbic acid and lactic acid, and sulphonic acids, such
as, for example, p-toluenesulphonic acid and 1,5-naphthalene-
disulphonic acid.

The salts of the compounds of the formula (I) can be
obtained in a simple manner by the usual methods of salt
formation, for example by dissolving a compound of the formula
(I) in a suitable inert solvent and adding the acid, for example
hydrochloric acid, and they can be isolated in a known manner,
for example, by filtration, and if appropriate purified by
washing with an inert organic solvent.

The compounds of the present invention display an anti-
microbial action, in particular an antimycotic action. They
possess a very broad antimycotic action spectrum, especially
against dermatophytes and blastomyces as well as biphase
fungi, for example against varieties of Candida, such as
Candida albicans, varieties of Epidermophyton, such as
Epidermophyton floccosum, varieties of Aspergillus, such as
Aspergillus niger and Aspergillus fumigatus, varieties of
Trichophyton, such as Trichophyton mentagrophytes, varieties
of Microsporon, such as Microsporon felineum and varieties of
Penicillium, such as Penicillium commune. The list of micro-
organisms in no way implies a limitation of the germs which
can be combated but is only illustrative.

Examples which may be mentioned of fields of application
in human medicine are: dermatomycoses and systemic mycoses
caused by Trichophyton mentagrophytes and other varieties
of Trichophyton, varieties of Microsporon, Epidermophyton
Floccosum, blastomyces and biphase fungi as well as moulds.

Examples which may be mentioned of fields of application
in veterinary medicine are: dermatomycoses and systemic mycoses,
especially those caused by the above-mentioned pathogens.

As stated above, the invention also relates to the
use in human and veterinary medicine of the compounds of
the invention.

The present invention provides a pharmaceutical compo-
sition containing as active ingredient a compound of the
invention in admixture with a solid or liquefied gaseous
diluent, or in admixture with a liquid diluent other than
a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose or, for example, a half, a third or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl
pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethyl glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C₁₄-alcohol with C₁₆-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams, and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polysamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.
The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention generally contain from 0.1 to 99.5% usually from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.
The discrete coherent portions constituting the medicament according to the invention will generally be adapted by virtue of their shape or packaging for medical administration and may be, for example, any of the following: tablets (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 2.5 g to 10 g of active ingredient.

The product of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition in the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in human and non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally, subcutaneously and intravenously), rectally or locally, preferably parenterally, especially intravenously. Preferred pharmaceutical compositions and medicaments are therefore those adapted for administration such as parenteral administration. Administration in the method of the invention is preferably parenteral administration.

In general it has proved advantageous to administer amounts of from 10 mg to 300 mg/kg, preferably 50 mg to 200 mg/kg, of body weight per day to achieve effective results. Nevertheless, it can at times be necessary to
deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some cases suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

The following Examples A, B and C illustrate the in vitro and in vivo activity of compounds of the present invention.

Example A

Antimycotic in vitro activity

Description of the experiment

The in vitro tests were carried out in a series dilution test with germ inocula of an average of $5 \times 10^4$ germs/ml of substrate. The nutrient medium was a) for dermatophytes and moulds: Sabouraud’s milieu d’épreuve and b) for yeasts: meat extract/glucose broth.

The incubation temperature was 27°C and the duration of incubation was 24 to 96 hours.

In these tests, the compounds according to the invention showed very good minimum inhibitory concentrations.

Example B

Antimicrobial in vivo activity (oral) in candidosis of mice

Description of the experiment

Mice of the SPF- CF$_1$ type were infected intravenously with $1-2 \times 10^6$ logarithmically growing Candida cells, which were suspended in physiological sodium chloride solution. The animals are treated orally one hour before and seven hours after the infection, with, in each case, 50 - 100 mg/kg of body weight of the formulations.

Result

Untreated animals died 3 to 6 days after infection. The survival rate on the 6th day after infection was about 5% in the case of untreated control animals.
In this test, the compounds according to the invention showed an action, which in some cases was very good (60 to 90% of survivors on the 6th day after infection), whilst Miconazol showed no action at these dosages.

It should be pointed out in particular, that some of the compounds according to the invention are also effective in the case of oral therapy of aspergillosis of mice.

Example C
Antimycotic in vivo activity (local) using experimental trichophytosis of guinea pigs as an example

Description of the experiment

White guinea pigs of the Pirbright-white strain were infected with a microconidia and macroconidia suspension of Trichophyton mentagrophytes on their shaved, non-scarified backs. The typical pattern of dermatophytosis with reddening, scaling and loss of hair up to total integumentary defect at the point of infection developed on the untreated animals within 12 days after infection. The infected animals were treated locally once daily, starting on the 3rd day after infection, with 1% strength solutions of the formulations according to the invention in polyethylene glycol.

On the 14th day after infection, the untreated control animals exhibited the typical pattern of dermatophytosis, whilst preparation examples 1, 2, 4, 8 and 10, for example, had partly to completely inhibited the course of the infection.

The following Examples illustrate the production of compounds of the present invention.

Example 1

\[ \text{OH} \quad \text{C} \quad \text{CH}_2 \quad \text{N} \quad \text{N} \]

(Process b)

20.2 g (0.297 mol) of imidazole are added to a solution of 9.5 g (0.175 mol) of sodium methylate in 49 ml of methyl alcohol. A solution of 44.3 g (0.135 mol) of 1-(4-biphenylyl)-2-chloro-1-(4-fluorophenyl)-ethanol in 103 mol of dimethylformamide is then added dropwise, and the reaction
mixture is heated to 60°C for 90 minutes. It is concentrated by distilling off the solvent in vacuo, and the residue is stirred with water. The crystals which remain are washed with acetonitrile and recrystallised from ethyl alcohol.

13.5 g (28% of theory) of 1-(4-biphenylyl)-1-(4-fluorophenyl)-2-(imidazol-1-yl)-ethanol of melting point 220°C are obtained.

Preparation of the starting material

34.5 g (0.15 mol) of 4-phenylphenacyl chloride are added in portions to a solution of 4-fluorophenyl-magnesium bromide, obtained from 7.3 g (0.33 mol) of magnesium and 52.5 g (0.3 mol) of 4-fluorobromobenzene in 100 ml of diethyl ether. After heating the reaction mixture under reflux for two hours, it is poured onto aqueous ammonium chloride solution. The ether phase is separated off, washed with water, dried over sodium sulphate and evaporated. 44.3 g of 1-(4-biphenylyl)-2-chloro-1-(4-fluorophenyl)-ethanol are obtained.

Example 2

(Process b)

Analogously to Example 1, 16.2 g (40% of theory) of 1-(2'-chloro-4-biphenylyl)-1-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-ethanol of melting point 190°C are obtained from 7.02 g (0.13 mol) of sodium metholate, 14.96 g (0.22 mol) of triazole, 40 g (0.1 mol) of 1-(2'-chloro-4-biphenyl-
yl)-2-chloro-1-(4-chlorophenyl)-ethanol, 36 ml of methyl alcohol and 75 ml of dimethylformamide, after heating the mixture to 70°C for 3 hours.

**Preparation of the starting material**

\[
\begin{align*}
\text{CHCl}_2\text{C} & \text{Cl} \\
\text{Cl} & \text{OH} \\
\end{align*}
\]

Analogously to Example 1, 75 g of 1-(2'-chloro-4-biphenylyl)-2-chloro-1-(4-chlorophenyl)-ethanol are obtained from 10.69 g (0.44 mol) of magnesium, 76.6 g (0.4 mol) of 4-bromochlorobenzene and 53 g (0.2 mol) of 4-(2-chlorophenyl)-phenacyl chloride.

\[
\begin{align*}
\text{Cl} & \text{COCH}_2\text{Cl} \\
\end{align*}
\]

293.7 g (2.2 mols) of aluminium chloride are introduced in portions to a solution of 377 g (2 mols) of 2-chlorobiphenyl in 160 ml (2 mols) of chloroacetyl chloride and 1,000 ml of methylene chloride. After 18 hours, the reaction mixture is poured onto ice and hydrochloric acid. The organic phase is separated off, washed, dried over sodium sulphate and concentrated in vacuo by distilling off the solvent. The oil which remains is purified by distillation. 478.7 g (90% of theory) of 4-(2-chlorophenyl)-phenacyl chloride of melting point 47°C are obtained.

**Example 3**

\[
\begin{align*}
\text{Cl} & \text{CH}_{2}\text{N} & \text{N} \\
\text{Cl} & \text{OH} \\
\end{align*}
\]
(Process a)

13.1 g (0.05 mol) of 4-biphenyl imidazol-1-yl-methyl ketone are added in portions to 21.6 g (0.1 mol) of 3-chlorophenyl-magnesium bromide (prepared from 2.4 g (0.1 mol) of magnesium and 19.1 g (0.1 mol) of 3-bromo-chlorobenzene) in 70 ml of ether. After adding 500 ml of dry toluene, the ether is distilled off and the suspension formed is treated with aqueous ammonium chloride solution. The toluene phase is separated off and filtered and the filtrate is dried over sodium sulphate. It is concentrated by distilling off the toluene in vacuo, and the crystalline residue is stirred with acetonitrile. After recrystallising the residue from ethanol, 9.4 g (50% of theory) of 1-(4-biphenyl)-1-(3-chlorophenyl)-2-(imidazol-1-yl)-ethanol of melting point 202°C are obtained.

The compounds in Table 1 below are obtained in a corresponding manner, either by process (a) or by process (b).

Table 1

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Az</th>
<th>Melting point (°C)</th>
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<tr>
<td>4</td>
<td>Cl</td>
<td>4-Cl</td>
<td>H</td>
<td>-</td>
<td>187</td>
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<tr>
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<td>Cl</td>
<td>Cl</td>
<td>4-Cl</td>
<td>H</td>
<td>206</td>
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<td>Cl</td>
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<td>Cl</td>
<td>4-Cl</td>
<td>H</td>
<td>176</td>
</tr>
<tr>
<td>8</td>
<td>4-Cl</td>
<td>Cl</td>
<td>H</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Example No.</td>
<td>R</td>
<td>R¹</td>
<td>R₂</td>
<td>R₃</td>
<td>Az</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>9</td>
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<td>4-Cl</td>
<td>H</td>
<td>N=N</td>
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<td>4-C</td>
<td>H</td>
<td>-</td>
<td>N=N</td>
</tr>
<tr>
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<td>-Cl</td>
<td>4-C</td>
<td>H</td>
<td>-</td>
<td>N=N</td>
</tr>
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<td>4-C</td>
<td>H</td>
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<td></td>
<td>Cl</td>
<td>4-Cl</td>
<td>H</td>
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<td></td>
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<td>-</td>
<td>N=N</td>
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<td>H</td>
<td>-</td>
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<td>H</td>
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<td>-</td>
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</tr>
<tr>
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<td>F</td>
<td>4-C</td>
<td>H</td>
<td>-</td>
<td>N=N</td>
</tr>
</tbody>
</table>
The present invention also comprises pharmaceutically acceptable bioprecursors of the active compounds of the present invention.

For the purposes of this specification the term 'pharmaceutically acceptable bioprecursor' of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to an animal or human being is converted in the patient's body to the active compound.
CLAIMS. The Claims defining the invention are as follows:

1. Compounds which are hydroxyethyl-azoles of the general formula

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\hline
\text{R} \\
\text{C} - \text{CH}_2 - \text{Az} \\
\text{OH}
\end{array}
\]

or a salt thereof

in which

Az represents imidazole or triazole,
R represents optionally substituted phenyl, naphthyl or tetrahydronaphthyl,
R\(^1\) represents optionally substituted phenyl or cycloalkyl and
R\(^2\) represents hydrogen, or
R\(^1\) and R\(^2\) together, in the o-position relative to one another, represent an optionally substituted methylene bridge with several members, or, together with the phenyl ring, represent naphthyl,
R\(^3\) represents halogen, alkyl, alkoxy or halogenoalkyl and
n represents 0, 1, 2 or 3.

2. Compounds according to claim 1 in which Az denotes an imidazol-1-yl, 1,2,4-triazol-1-yl or 1,3,4-triazol-1-yl radical, R denotes an optionally substituted phenyl, naphthyl or tetrahydronaphthyl radical, R\(^1\) denotes an optionally substituted phenyl or C\(_3\) to C\(_7\) cycloalkyl radical, and R\(^2\) denotes a hydrogen atom, or R\(^1\) and R\(^2\) together, in the ortho-position relative to one another, denote a methylene bridge which has 3 to 5 methylene groups and is optionally monosubstituted or polysubstituted, or R\(^1\) and R\(^2\) together with the phenyl ring, complete a naphthyl radical, R\(^3\) denotes a halogen atom, a straight-chain or branched alkyl or alkoxy group with in each case 1 to 4 carbon atoms, or a halogenoalkyl group with 1 to 4 carbon atoms and up to 5 halogen atoms, and n is 0, 1 or 2.

3. Compounds according to claim 1 in which Az denotes an imidazol
-l-yl or 1,2,4-triazol-1-yl radical, \( R \) denotes a phenyl radical, which is optionally monosubstituted or disubstituted by chlorine, fluorine or methyl, or denotes a naphthyl or tetrahydronaphthyl radical, \( R^1 \) denotes a phenyl, cyclopentyl or cyclohexyl radical, which is optionally monosubstituted or disubstituted by chlorine, bromine, fluorine or methyl, and \( R^2 \) denotes a hydrogen atom, or \( R^1 \) and \( R^2 \) together, in the ortho-position relative to one another, denote a trimethylene, tetramethylene or pentamethylene bridge, which is optionally substituted by chlorine or methyl, or, together with the phenyl ring, complete a naphthyl radical, \( R^3 \) denotes a chlorine or fluorine atom or a methyl group, and \( n \) is 0 or 1.

4. Compounds according to claim 1 as hereinbefore specifically identified in any of Examples 18 to 27.

5. Compounds according to claim 1 as hereinbefore specifically identified other than the compounds claimed in claim 4.

6. A process for the production of compounds as claimed in any of claims 1 to 5 in which:

a) an azolylmethyl phenyl ketone of the general formula

\[
\text{Az} - \text{CH}_2 - \text{Az} \tag{II}
\]

in which

\( \text{Az} \), \( R^1 \), \( R^2 \), \( R^3 \) and \( n \) have the same meaning as in claim 1,

is reacted with a Grignard compound of the general formula

\[
\text{R - Mg - X} \tag{III}
\]

in which

\( \text{R} \) has the same meaning as in claim 1 and

\( \text{X} \) denotes a halogen atom,

in the presence of a diluent, or

b) a 1-halogeno-ethan-2-ol of the general formula
in which
R, R⁴, R⁵, R⁶, R⁷ and n have the same meaning as in claim 1, and
Y denotes a halogen atom,
is reacted with an azole of the general formula

\[ Z - Azo \]  

(V)
in which
Az has the same meaning as in claim 1 and
Z denotes a hydrogen atom or an alkali metal,
and the product of process variant (a) or (b) is converted, if desired, into a salts by reaction with an acid.

7. A process according to claim 6 (a) in which X denotes a chlorine or bromine atom.

8. A process according to claim 6 (a) or 7 in which the reaction is carried out at 30 to 80°C.

9. A process according to claim 6 (b) in which Y denotes a chlorine or bromine atom.

10. A process according to claim 6 (b) or 9 in which the reaction is carried out in the presence of an acid-binding agent.

11. A process according to any of claims 6(b), 9 and 10 in which the reaction is carried out in the presence of a diluent.

12. A process according to any of claims 6(b) and 9 to 11 in which the reaction is carried out at 30 to 200°C.

13. A process for the production of a compound according to claim 1 substantially as hereinbefore described in any of Examples 1, 2 and 4 to 17.

14. A process for the production of a compound according to claim 1 substantially as hereinbefore described in any of Examples 3 and 18 to 29.
15. Compounds according to claim 1 whenever prepared by a process according to any one of claims 6 to 14.

16. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 5 and 15 in admixture with a solid, or liquefied gaseous, or liquid diluent.

17. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 5 and 15 in the form of a sterile or physiologically isotonic aqueous solution.

18. A medicament in dosage unit form, or in the form of tablets, pills, dragees, capsules, ampoules or suppositories, comprising a compound according to any one of claims 1 to 5 and 15.

19. A method of combating mycoses in human and non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 5 and 15 either alone or in admixture with a diluent or in the form of a medicament according to claim 18.

20. A composition according to claim 16 or 17, or a medicament according to claim 18, or a method according to claim 19, substantially as herein described with reference to any one of the foregoing specific examples thereof.

21. A compound of the formula (II), or (IV).

22. A process, substantially as herein described, of preparing a compound according to claim 21.

23. A pharmaceutically acceptable bioprecursor substantially as herein described.

DATED this 23rd day of November, 1979.

BAYER AKTIENGESELLSCHAFT,
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.