

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

CL Pharma Aktiengesellschaft, of St. Peter-Strasse 25, A-4021 Linz, AUSTRIA,
hereby apply for the grant of a standard patent for an invention entitled:

Antimycotic Aminoazoles I

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No: Country: Application Date:
P 36 44 616.5 FEDERAL REPUBLIC OF GERMANY 29 December 1986

The address for service is:-

APPLICATION ACCEPTED AND AMENDMENTS

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

ALLOWED 14.12.89

DATED this TWENTY THIRD day of DECEMBER 1987

CL Pharma Aktiengesellschaft

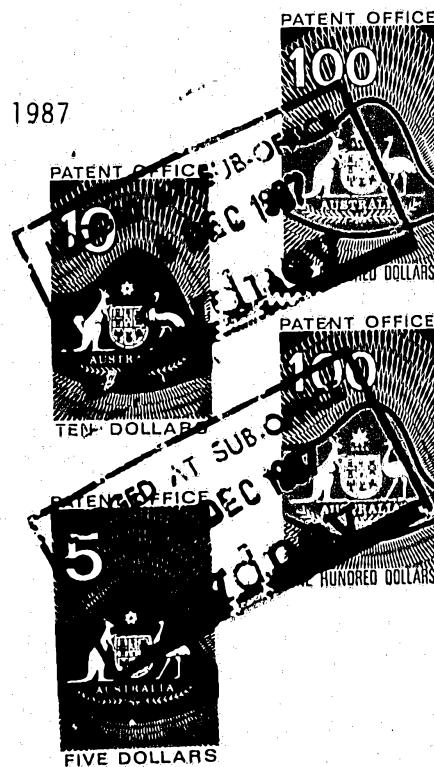
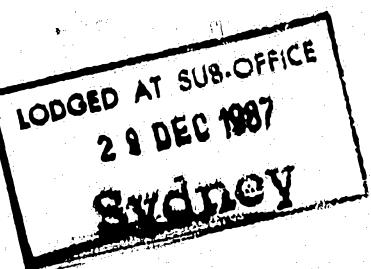
By: *M. J. Anderson*

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 46338
S&F CODE: 52605

| | | |
|-----------------------|-----|----------|
| FEE STAMP TO VALUE OF | 215 | ATTACHED |
| MAIL OFFICER | | |

5845/10



SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Antimycotic Aminoazoles I

Both care
*We, Klaus RODEN, Peter SEIDEL.....
[full name of declarant(s)]
of CL Pharma Aktiengesellschaft
..... St.Peter-Straße 25, A-4021 Linz, Austria.....
[full address of declarant(s) - not post office box]

do solemnly and sincerely declare as follows:-

1. ~~We~~ We are authorised by CL Pharma Aktiengesellschaft, the applicant for the patent to make this declaration on its behalf.
2. The basic application as defined by Section 141 of the Act was made in Federal Republic of Germany on 29 December 1986 by Lentia Gesellschaft mit beschränkter Haftung, Chem. u. pharm. Erzeugnisse - Industriebedarf.
3. Karl Schermanz; Gerald Saischek; Robert Urmann; and Kurt Martetschlager, of Gaußgasse 4/10/54, A-8010 Graz; Roseggerstrasse 4, A-4600 Wels; Wankmüllerhofstrasse 74, A-4020 Linz; and Himmelbergerstrasse 14, A-4020 Linz, all in Austria [respectively], are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

Lentia Gesellschaft mit beschränkter Haftung, Chem. u. pharm. Erzeugnisse - Industriebedarf, Arabellastrasse 4, D-8000 München 81, Federal Republic of Germany filed the basic application as assignee of Chemie Linz Aktiengesellschaft, St.Peter-Strasse 25, A-4021 Linz, Austria. Chemie Linz AG was entitled by Contract of Employment between the inventors as employees and Chemie Linz AG as employer. Lentia Gesellschaft mit beschränkter Haftung assign their rights including the priority rights accruing from the basic application to the applicant, CL Pharma Aktiengesellschaft. This company was separated from Chemie Linz AG and is now registered as an individual company.

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

DECLARED at Linz this 2nd day of March 19 88

CL PHARMA AKTIENGESELLSCHAFT

Signature of Declarant

Klaus Roden Peter Seidel

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

JTA:295U

(12) PATENT ABRIDGMENT (11) Document No. AU-B-83095/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 593969

(54) Title

ANTIMYCOTIC AMINOAZOLES I

International Patent Classification(s)

(51)⁴ C07D 233/61 A61K 031/44 C07D 401/12 C07D 409/14
A61K 031/415

(21) Application No. : 83095/87

(22) Application Date : 29.12.87

(30) Priority Data

(31) Number (32) Date (33) Country
3644616 29.12.86 DE FEDERAL REPUBLIC OF GERMANY

(43) Publication Date : 30.06.88

(44) Publication Date of Accepted Application : 22.02.90

(71) Applicant(s)

CL PHARMA AKTIENGESELLSCHAFT

(72) Inventor(s)

KARL SCHERMANZ; GERALD SAISCHEK; ROBERT URMANN; KURT
MARTETSCHLAGER

(74) Attorney or Agent

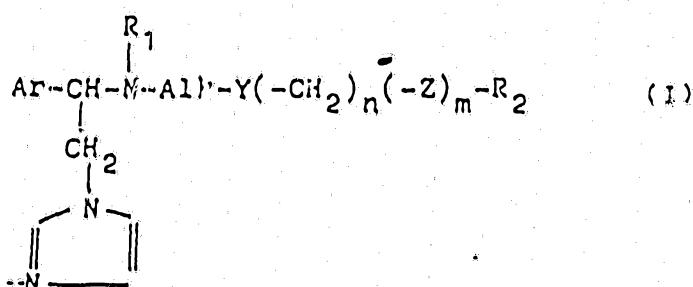
SPRUSON & FERGUSON

(56) Prior Art Documents

AU 462239 32467/71 09.62-42, 09.18, 87.19
GB 2136801

(57) Claim

1. An imidazole derivative of the formula



in which Ar denotes phenyl, biphenyl, naphthyl or thienyl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, R₁ denotes hydrogen or lower alkyl, Alk denotes straight-chain or branched alkylene having 1 to 10 carbon atoms, Y denotes oxygen, sulfur, sulfinyl or sulfonyl, n denotes one of the numbers

(11) AU-B-83095/87

-2-

(10) 593969

0, 1 or 2, Z denotes sulfur or sulfinyl, m denotes the number 0 or 1, m being the number 0 when Y denotes sulfur, sulfinyl or sulfonyl, and m being the number 1 when Y denotes oxygen, and R₂ denotes cyclohexyl, or denotes phenyl or naphthyl, each of which is optionally substituted by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy, or denotes biphenylyl or pyridyl, and its pharmaceutically acceptable acid addition salts.

S & F Ref: 46338

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

593969

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:

Accepted:

Published:

This document contains the
amendments made under
Section 49 and is correct for
printing.

Priority:

Related Art:

Name and Address

of Applicant:

CL Pharma Aktiengesellschaft
St. Peter-Strasse 25
A-4021 Linz
AUSTRIA

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

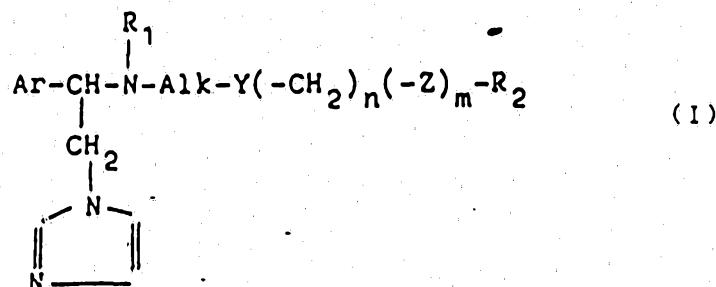
Complete Specification for the invention entitled:

Antimycotic Aminoazoles I

The following statement is a full description of this invention, including the best method of performing it known to me/us

Abstract of the disclosure

New imidazole derivatives of the general formula

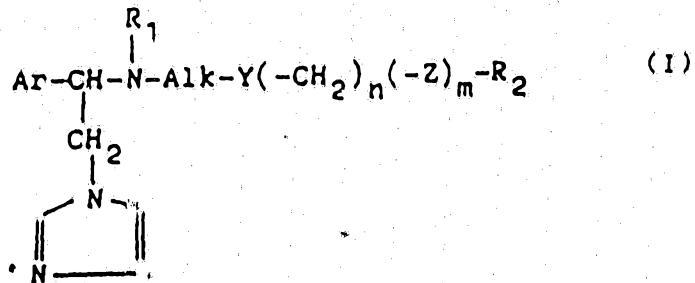


in which Ar denotes phenyl, biphenyl, naphthyl or thieryl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, R₁ denotes hydrogen or lower alkyl, Alk denotes straight-chain or branched alkylene having 1 to 10 carbon atoms, Y denotes oxygen, sulfur, sulfinyl or sulfonyl, n denotes one of the numbers 0, 1 or 2, Z denotes sulfur or sulfinyl, m denotes the number 0 or 1, m being the number 0 when Y denotes sulfur, sulfinyl or sulfonyl, and m being the number 1 when Y denotes oxygen, and R₂ denotes cyclohexyl, phenyl or naphthyl, each of which is optionally substituted by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy, or denotes biphenyl or pyridyl, and processes for their preparation. The imidazole derivatives have excellent antimycotic properties for use in human and veterinary medicine.

The invention relates to new imidazole derivatives, processes for the preparation thereof, and antimycotics containing them, and processes for the preparation thereof.

5 EP-A-183,147 describes β -substituted aminophenylazole derivatives which are used as fungicides for agriculture and horticulture. However, the principle of constructing 2-thioalkylaminoethylimidazoles is not published. It is disclosed in H. Büchel: Fungicide Chemistry: Advances and Practical Applications, Am.Chem.Soc. Washington 1986, pages 11 - 23 and G. Jäger, Pesticide Chemistry: Human Welfare and the Environment, Vol. I, 10 55-56, Pergamon Press Oxford, 1983, that, despite great structural similarity within the azole class of compounds, 15 there are often great differences in the biological properties. It has now been found, surprisingly, that new imidazole derivatives have excellent antimycotic properties on use in human and veterinary medicine.

Accordingly, the invention relates to imidazole 20 derivatives of the general formula



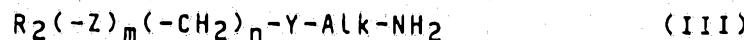
in which Ar denotes phenyl, biphenyl, naphthyl or 25 thienyl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, R₁ denotes hydrogen or lower alkyl, Alk denotes straight-chain or branched alkylene having 1 to 10 carbon atoms, Y denotes oxygen, sulfur, sulfinyl or sulfonyl, n denotes one of the numbers 0, 1 or 2, Z denotes sulfur or sulfinyl, m denotes the number 0 or 1, m being the number 0 when Y 30 denotes sulfur, sulfinyl or sulfonyl, and m being the number 1 when Y denotes oxygen, and R₂ denotes cyclohexyl,

or denotes phenyl or naphthyl, each of which is optionally substituted by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy, or denotes biphenyl or pyridyl, and to their pharmaceutically acceptable acid addition salts.

It has further been found that the substances according to the invention are obtained by reacting compounds of the general formula II

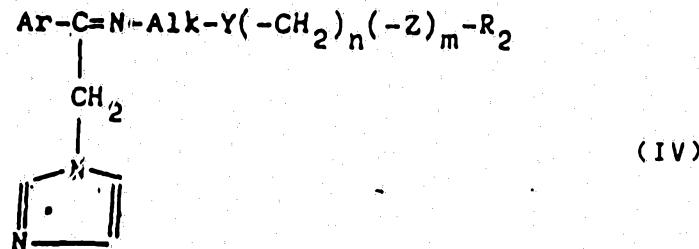


10 in which Ar has the above meaning, with compounds of the general formula III



in which R_2 , Z , m , n , Y and Alk have the above meaning, where appropriate in the presence of an inert diluent,

15 reducing the resulting imino compounds of the general formula IV



in which Ar, Alk, Y, Z, R_2 , n and m have the above meaning, where appropriate in the presence of an inert diluent, and, if desired, converting the resulting compounds of the formula I in which R_1 denotes hydrogen, by customary alkylation methods, into compounds of the formula I in which R_1 denotes lower alkyl.

The reaction of the compounds II and III is

carried out, for example, by heating the reaction mixture in an organic diluent. If compounds III are used in the form of their salts, it is necessary to add one equivalent of a base such as trialkylamine, sodium alcoholate 5 or alkali metal hydroxide.

Diluents which are used are aliphatic or aromatic hydrocarbons, which may be chlorinated, such as petroleum fractions, perchloroethylene, benzene, toluene, chlorobenzene, xylene, ethers such as dibutyl ether or dioxane, 10 alcohols such as butanol, pentanol or ethylene glycol, amides such as dimethylformamide, and mixtures thereof with the abovementioned diluents. The components are heated under reflux with a water trap until no more water of reaction separates out. The imino compound IV 15 obtained after removal of the diluent is dissolved or suspended in an organic diluent, followed by cooling. Diluents which are used are, in particular, alcohols, preferably methanol, or ethers such as diethyl ether or tetrahydrofuran. The reduction is then carried out by 20 addition of a reducing agent, in particular a complex metal hydride such as, for example, alkali metal borohydride, alkali metal cyanoborohydride, aluminum borohydride or lithium aluminum hydride, preferably sodium borohydride, at a temperature of, say, between -20°C and 25 the reflux temperature of the diluent used, preferably at a temperature of -5°C to +20°C.

All conventional methods of alkylation are suitable for introducing the alkyl radical R_1 . For example, to introduce the methyl radical it is possible to add 30 aqueous formaldehyde solution to a compound of the formula I in which R_1 denotes hydrogen in an alcoholic, for example methanolic, solution, to heat the mixture to boiling, and, after the reaction solution has cooled, to allow a reducing agent, preferably sodium borohydride, to 35 act on it.

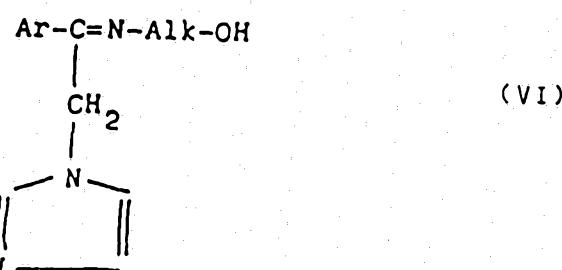
In another process, the substances according to the invention are obtained by reacting a compound of the general formula II with an aminoalkanol of the general

formula V



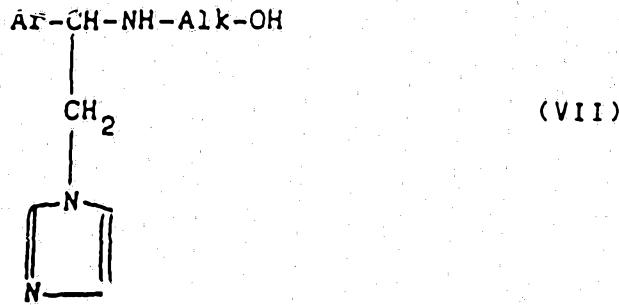
reducing the imino compound which is obtained as reaction product of the general formula VI

5



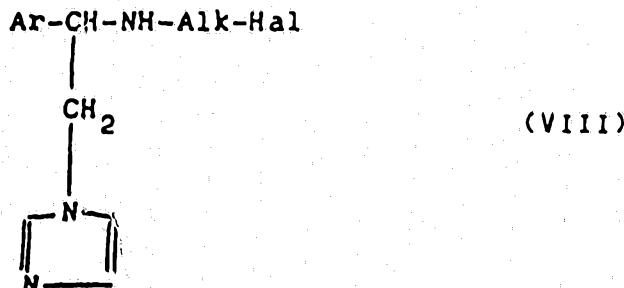
converting the resulting hydroxyalkylamino compound of the general formula VII

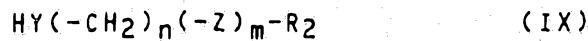
10



into the corresponding halogenoalkylamino compound of the general formula VIII

reacting the latter with a compound of the general formula IX





and, if desired, converting the resulting compounds of the formula I in which R_1 denotes hydrogen, by customary alkylation methods, into compounds of the formula I in which R_1 denotes lower alkyl, where Ar, Alk, Y, Z, R_2 , n and m in the above formulae V to IX have the meaning indicated for formula I, and Hal represents halogen.

The reaction of a compound of the general formula II with an amino alcohol of the general formula V is carried out in an organic diluent at a temperature between 0°C and 180°C , preferably at the reflux temperature of the diluent used. The diluents which are used are aliphatic or aromatic hydrocarbons, which may be chlorinated, such as petroleum fractions, perchloroethylene, benzene, toluene, xylene, chlorobenzene, ethers such as dibutyl ether or dioxane, alcohols such as butanol, pentanol or ethylene glycol, amides such as dimethylformamide, and mixtures thereof with the abovementioned diluents. The imino compound VI obtained after removal of the diluent is dissolved or suspended in an organic diluent, and the solution or suspension is cooled. The diluents which are used are, in particular, alcohols, preferably methanol, or ethers such as diethyl ether or tetrahydrofuran. The reduction is carried out by addition of a reducing agent, preferably a complex metal hydride, in particular sodium borohydride, at a temperature from about -20°C to the reflux temperature of the diluent used, preferably at a temperature of about -5°C to $+20^{\circ}\text{C}$. The hydroxyalkylamino compound VII which is obtained after the customary working up is dissolved in an organic diluent, preferably in a chlorinated aliphatic hydrocarbon, for example chloroform, and the solution is cooled. The hydroxyl compound VII is converted into the corresponding halogen compound VIII by addition of a halogenating agent, for example phosphorus tribromide, the reaction being carried out at a temperature of about

-50°C to room temperature, preferably from -20°C to 0°C. The reaction of the halogenoalkylamino compound VIII with the compound of the general formula IX is preferably carried out in alcoholic, for example methanolic, solution in the presence of a base, for example sodium methylate or alkali metal hydroxide, at a temperature of about -20°C to 120°C, preferably at a temperature of 20°C to 80°C.

R₁ in the formulae I to IX denotes a hydrogen atom or an alkyl radical having 1 to 4 C atoms, preferably a hydrogen atom or the methyl radical. Ar denotes phenyl, biphenyl, naphthyl or thienyl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, preferably 2,4-dichlorophenyl.

Alk denotes a straight-chain or branched, saturated hydrocarbon radical having 1 to 10 C atoms. Examples of such radicals are methyl, ethyl, n-propyl, i-propyl, butyl, s-butyl, t-butyl radicals, and straight-chain or branched pentyl, hexyl, heptyl and octyl radicals.

Y denotes sulfur, sulfinyl or sulfonyl, particularly preferably sulfur, as well as oxygen when m is equal to 1. Z can denote sulfur or sulfinyl. R₂ denotes a cyclohexyl radical, phenyl or naphthyl radicals, either of which may be substituted once or several times by halogen atoms, hydroxyl groups, alkyl or alkoxy radicals having 1-4 C atoms, or trifluoromethyl, or denotes biphenyl or pyridyl, preferably 4-chlorophenyl, 4-bromophenyl, cyclohexyl or naphthyl.

The compounds according to the invention and their pharmacologically tolerated salts have interesting antimycotic properties and can be used as medicaments in human and veterinary medicine. This action has been demonstrated by determination of the minimum inhibitory concentration (MIC) for yeasts, molds and dermatophytes.

The active compounds according to the invention can be used in the customary manner as solid, semisolid or liquid formulations in the form of tablets, capsules, powders, suppositories, solutions, creams, lotions, gels,

ointments or the like. Examples of pharmaceutically tolerated non-toxic vehicles or excipients which are normally used for solid formulations are tricalcium phosphate, calcium carbonate, kaolin, bentonite, talc, 5 gelatin, lactose and starch. Examples of those suitable for semisolid formulations are water, vegetable oils and low-boiling solvents such as i-propanol, hydrogenated naphthalenes and the like.

The pharmaceutical agents containing the active 10 compounds according to the invention can be subjected to conventional pharmaceutical measures, such as sterilization, and can contain conventional pharmaceutical additives such as preservatives, stabilizers, emulsifiers, salts for adjusting the osmotic pressure, and buffers. 15 The agents can also contain other therapeutically active materials besides the compounds according to the invention.

The agents containing the compounds according to the invention are normally composed of a pharmaceutically 20 tolerated non-toxic vehicle in conjunction with one or more compounds according to the invention in an effective amount which results in alleviation or prevention of the specific conditions to be treated. Since the active compounds according to the invention exhibit an anti- 25 mycotic action over a wide concentration range, the effective amount may vary. For example, the amount for topical formulations may be approximately 0.1 to 10% of the total pharmaceutical formulation, whereas in other formulations the amount may be approximately 5 to about 30 95% or more. It is preferable, to facilitate administration, to formulate the pharmaceutical agents according to the invention as dosage unit.

The compounds and agents according to the invention can be administered for pharmaceutical use in humans 35 and animals in a conventional manner, for example: topically, orally, parenterally or in a similar manner. The exact schedule for the pharmaceutical administration of the compounds and agents according to the invention

necessarily depends on the requirements of the individual case, the nature of the treatment, which, for example, may be preventive or curative, and the nature of the organisms involved.

5 For systemic, for example oral or parenteral, administration, it is generally appropriate to administer the active compound in amounts of about 1 - 120 mg/kg of body weight per day, preferably 5 - 100 mg/kg of body weight per day, it also being possible to distribute 10 these amounts over several doses (for example 3 per day) in order to achieve good results. However, for localized administration correspondingly less active compound is necessary.

Example 1 (Compound No. 23):

15 a) Preparation of the intermediate

1-(2-(2,4-Dichlorophenyl)-2-(3-(4-bromophenylthio)propyl-imino)ethyl)-1H-imidazole

14.8 g (0.058 mole) of 2,4-dichlorophenacyl-imidazole, 16.8 g (0.059 mole) of 4-bromophenylthio-

20 propylamine hydrochloride and 6.0 g (0.059 mole) of triethylamine are suspended or dissolved in 100 ml of toluene, and the mixture is heated under reflux with a water trap until no more water of reaction separates out. The reaction solution is then washed with water, the org.

25 phase is dried with sodium sulfate and, after the solvent has been evaporated off, 27.9 g of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-bromophenylthio)propylimino)ethyl)-1H-imidazole are obtained as a viscous oil (yield: 98%).

b) Preparation of the final product

30 1-(2-(2,4-Dichlorophenyl)-2-(3-(4-bromophenylthio)propyl-amino)ethyl)-1H-imidazole

27.9 g (0.057 mole) of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-bromophenylthio)propylimino)ethyl)-1H-imidazole

are dissolved in 150 ml of methanol, the solution is

35 cooled to -5°C, and 6.4 g (0.169 mole) of sodium borohydride are added in portions in such a way that the temperature does not rise above 5°C. The reaction mixture is subsequently stirred at 30°C for 1 hour, then

evaporated to dryness and the pH is adjusted to 1 with half-concentrated hydrochloric acid. Subsequently the reaction solution is adjusted to a pH of about 12 with 40% strength sodium hydroxide solution and is extracted 5 several times with dichloromethane. After the combined extracts have been washed with water and dried, and the solvent has been removed in vacuo there is obtained an oil from which, by treatment with acetone and nitric acid, 10.6 g of pure dinitrate of 1-(2-(2,4-dichloro-10 phenyl)-2-(3-(4-bromophenylthio)propylamino)ethyl)-1H-imidazole of melting point 162 - 179°C are obtained (yield: 32%).

Example 2 (Compound No. 20):

a) Preparation of the intermediate

15 1-(2-(2,4-Dichlorophenyl)-2-(3-hydroxypropylimino)ethyl)-1H-imidazole

153.2 g (0.60 mole) of N-(2,4-dichlorophenacyl)-imidazole and 53.0 g (0.705 mole) of 3-amino-1-propanol are suspended or dissolved in 400 ml of toluene, and the 20 mixture is heated under reflux with a water trap until no more water of reaction separates out. The reaction solution is then washed 3 times with water, the organic phase is dried with sodium sulfate and, after the solvent has been evaporated off, 179 g of 1-(2-(2,4-dichlorophenyl)-25 2-(3-hydroxypropylimino)ethyl)-1H-imidazole are obtained as a highly viscous oil. (Yield: 95.6%).

1-(2-(2,4-Dichlorophenyl)-2-(3-hydroxypropylamino)ethyl)-1H-imidazole

179.0 g (0.5737 mole) of 1-(2-(2,4-dichloro-30 phenyl)-2-(3-hydroxypropylimino)ethyl)-1H-imidazole are dissolved in 300 ml of methanol, the solution is cooled to 0°C, and 50.0 g (1.322 mole) of sodium borohydride are added in portions in such a way that the temperature does not rise above 5°C. After the borohydride has 35 been added, the reaction mixture is stirred at room temperature for a further 2 hours, then evaporated to dryness, and the pH is adjusted to 1 with half-concentrated hydrochloric acid. Subsequently, the reaction solution

is adjusted to a pH of about 12 with 40% strength sodium hydroxide solution, and is extracted several times with dichloromethane. After the combined organic extracts have been washed with water and dried, and the solvent

5 has been removed in vacuo, 169 g of crude product are obtained as an oil. Recrystallization of the oil from acetone results in 107 g of pure 1-(2-(2,4-dichlorophenyl)-2-(3-hydroxy-propylamino)ethyl)-1H-imidazole of melting point 77-79°C. (Yield: 51%).

10 1-(2-(2,4-Dichlorophenyl)-2-(3-bromopropylamino)ethyl)-1H-imidazole

12.6 g (0.04 mole) of 1-(2-(2,4-dichlorophenyl)-2-(3-hydroxypropylamino)ethyl)-1H-imidazole are dissolved in 30 ml of chloroform, and the solution is cooled to -5°C. While stirring, 10.83 g of phosphorus tribromide, dissolved in 20 ml of CHCl_3 , are slowly added dropwise in such a way that the temperature does not rise above 0°C. After the dropwise addition, 100 ml of netroleum ether are added to the reaction mixture, resulting in 15 20.5 g of crystalline 1-(2-(2,4-dichlorophenyl)-2-(3-bromopropylamino)ethyl)-1H-imidazole as the dihydروبromide of melting point 140 - 150°C, and this is immediately reacted further, for reasons of stability. (Yield: 95%).

25 b) Preparation of the final product

1-(2-(2,4-Dichlorophenyl)-2-(3-(4-chlorophenylthio)-propylamino)ethyl)-1H-imidazole

5.4 g (0.01 mole) of freshly prepared 1-(2-(2,4-dichlorophenyl)-2-(3-bromopropylamino)ethyl)-1H-imidazole dihydروبromide and 1.45 g (0.01 mole) of 4-chlorothiophenol are dissolved in 50 ml of methanol, and 6 ml of a 30% strength solution of sodium methylate are added. The reaction mixture is heated to reflux for 2 hours and then stirred at room temperature for a further 14 hours. Subsequently the methanol is evaporated off in vacuo, the residue is taken up in dichloromethane, and the organic phase is shaken with 5% strength sodium hydroxide solution and washed with water. After drying and removal of the

solvent in vacuo, the residue is dissolved in acetone, and concentrated nitric acid is added dropwise, resulting in 3.0 g of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-chlorophenylthio)propylamino)ethyl)-1H-imidazole as the di-nitrate. Recrystallization from alcohol results in 2.2 g of colorless crystals of melting point 168 - 177°C. (Yield: 41%).

Example 3 (Compound No. 36):

Preparation of the N-alkyl compounds

10 1-(2-(2,4-Dichlorophenyl)-2-(N-methyl-3-(4-chlorobenzylthio)propylamino)ethyl)-1H-imidazole

8.18 g (0.018 mole) of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-chlorobenzylthio)propylamino)ethyl)-1H-imidazole are dissolved in 100 ml of methanol, 34.3 g of 35% strength aqueous formaldehyde solution are added, and the

15 mixture is boiled for 2 hours. The reaction solution is cooled and then 14.6 g of sodium borohydride are added, and the mixture is stirred at room temperature for 14 hours. Subsequently the methanol is evaporated off in

20 vacuo, half-concentrated hydrochloric acid is added to the residue, and then 40% strength sodium hydroxide solution is added until the pH is 12, and the mixture is extracted 3 times with dichloromethane. The combined extracts are washed with water and then the solvent is

25 evaporated off in vacuo, resulting in an oil. The crude product is chromatographed on silica gel (mobile phase: ethyl acetate/methanol = 10 : 1). An oil is obtained and is treated with ethanolic hydrochloric acid to result in 2.0 g of 1-(2-(2,4-dichlorophenyl)-2-(N-methyl-3-(4-

30 chlorobenzylthio)propylamino)ethyl)-1H-imidazole as the dihydrochloride of melting point 170 - 180°C. (Yield: 21%).

The following compounds were obtained by one of the indicated processes:

Table I

| No. | Ar | R ₁ | Alk | Y | n | Z | R ₂ | Salt | Melting point °C |
|-----|--------------------|----------------|------------------------------------|---|---|---|--------------------------|---|---------------------|
| 1 | 4-chlorophenyl | H | -(CH ₂) ₂ - | S | - | - | 4-chlorophenyl | 2HCl-H ₂ O | 124-127 |
| 2 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | - | - | cyclohexyl | 2HNO ₃ | 149-160 |
| 3 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | - | - | 4-chlorophenyl | 2HCl | 206-212 |
| 4 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | - | - | 4-bromophenyl | 2HNO ₃ | 183-186 |
| 5 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | - | - | 4-methoxyphenyl | 2HNO ₃ | 163-174 |
| 6 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | - | - | 2-naphthyl | 2HNO ₃ | 188-195 |
| 7 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | 1 | - | phenyl | 2H ₂ C ₂ O ₄ -H ₂ O | 156 |
| 8 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | 1 | - | phenyl | - | viscous oil |
| 9 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | 1 | - | 4-chlorophenyl | 2HNO ₃ | 157-161 |
| 10 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | S | 1 | - | 3-trifluoromethyl-phenyl | - | viscous oil |
| 11 | 4-bromophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | - | viscous oil |
| 12 | 4-methylphenyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | - | viscous oil |
| 13 | 4-methoxyphenyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | - | viscous oil |
| 14 | 4-biphenyl | H | -(CH ₂) ₂ - | S | - | - | 4-chlorophenyl | 2HCl | 190-197 |
| 15 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | cyclohexyl | 2HNO ₃ | 170-174 |
| 16 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | phenyl | 2HCl-H ₂ O | resin |
| 17 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-methylphenyl | 2HNO ₃ | 196-200 |

| No. | Ar | R ₁ | Alk | Y | n | z | R ₂ | Salt | Melting point °C |
|-----|--------------------|-----------------|------------------------------------|-----------------|---|---|--------------------|-----------------------------|-----------------------|
| 18 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-fluorophenyl | 2HNO ₃ | 160-165 |
| 19 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | 2HCl | 193-200 |
| 20 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | 2HNO ₃ | 168-177 |
| 21 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | SO | - | - | 4-chlorophenyl | - | viscous oil |
| 22 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | SO ₂ | - | - | 4-chlorophenyl | - | viscous oil |
| 23 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-bromophenyl | 2HNO ₃ | 162-179 |
| 24 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-bromophenyl | 2HCl | 178-187 |
| 25 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-phenyl | 2HCl | 202-216 |
| 26 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 2,6-dichlorophenyl | 2HNO ₃ | 180-190 |
| 27 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 2-naphthyl | 2HNO ₃ | 196 |
| 28 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 2-pyridyl | - | viscous oil |
| 29 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 2-pyridyl | 2HNO ₃ | 178-179 |
| 30 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | - | - | 4-pyridyl | 3HCl 2.5H ₂ O | deliquescent resin |
| 31 | 2-thienyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | - | viscous oil |
| 32 | 1-naphthyl | H | -(CH ₂) ₃ - | S | - | - | 4-fluorophenyl | HCl | 153-156 |
| 33 | 1-naphthyl | CH ₃ | -(CH ₂) ₃ - | S | - | - | 4-fluorophenyl | 2HCl | 175-190 |
| 34 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | 1 | - | phenyl | 2HNO ₃ | 128-137 |
| 35 | 2,4-dichlorophenyl | H | -(CH ₂) ₃ - | S | 1 | - | 4-chlorophenyl | 2HNO ₃ | 108-133 |
| 36 | 2,4-dichlorophenyl | CH ₃ | -(CH ₂) ₃ - | S | 1 | - | 4-chlorophenyl | 2HCl | 170-180 |
| 37 | 2,4-dichlorophenyl | H | 2-butylene | S | - | - | 4-chlorophenyl | 2HNO ₃ | 143-147 |

| No. | Ar | R ₁ | ALK | Y | n | z | R ₂ | Salt | Melting point °C |
|-----|--------------------|----------------|------------------------------------|---|---|----|----------------|-------------------|---------------------|
| 38 | 2,4-dichlorophenyl | H | -(CH ₂) ₅ - | S | - | - | 4-chlorophenyl | 2HNO ₃ | 156-161 |
| 39 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | O | 2 | S | 4-chlorophenyl | 2HNO ₃ | 81-85 |
| 40 | 2,4-dichlorophenyl | H | -(CH ₂) ₂ - | O | 2 | SO | 4-chlorophenyl | - | resin |
| 41 | 1-naphthyl | H | -(CH ₂) ₃ - | S | - | - | 4-chlorophenyl | HCl | 172-176 |

Example A

Tablet containing 200 mg of active compound for oral administration

2 g of compound No. 19 and 1 g of lactose were
5 granulated with 1 ml of 10% strength aqueous polyvinyl-
pyrrolidone K25 solution. The mixture was forced through
a screen of mesh size 3 - 5 mm and was dried. This dried
mixture was homogenized through a screen of mesh size
0.8 - 1.25 mm and then mixed with 0.58 g of microcrystal-
10 line cellulose (Avicel PH102), 30 mg of Na carboxymethyl
starch and 2 mg of magnesium stearate. The resulting
mixture was compressed to 10 tablets.

Example B

1% strength solution for topical treatment

15 Sufficient polyethylene glycol 400 was added to
a solution of 1 g of compound No. 19 in 50 ml of purified
water to produce a total of 100 ml of solution.

Example C

1% ointment for topical treatment

20 66 g of liquid petrolatum were melted on a water-
bath with 3.5 g of Alfol 16 (cetyl alcohol) and 0.1 g of
cholesterol, and a solution of 1 g of compound No. 19 in
29.4 g of purified water was added. While cooling slowly,
this mixture was homogenized to produce 100 g of ointment.

25 Example D

1% injection solution (ampoules containing 100 mg of
active compound)

30 3 g of compound No. 19 and 0.3 g of a mixture of
2 parts of methyl p-hydroxybenzoate and one part of
propyl p-hydroxybenzoate were dissolved and made up to
300 ml with water for injection, and the solution was
filtered through a membrane filter of pore size 0.2 μ m
to sterilize and remove particles and then dispensed into
10 ml ampoules under aseptic conditions.

35 Example E:

The antimycotic activities of the compounds were
measured by in vitro determination of the minimum inhibitory
concentration (MIC) for yeasts, molds and dermatophytes.

6 dermatophytes, 2 yeasts and 4 molds were used for testing with fungi, as follows:

| | | |
|----|-----------------------------|-----------------------|
| | Trichophyton mentagrophytes | (Tri.me.) |
| 5 | Trichophyton rubrum | (Tri.ru.) |
| | Trichophyton verrucosum | (Tri.ve.) |
| | Microsporum canis | (Mi.can.) |
| | Epidermophyton floccosum | (Ep.flo.) |
| | Microsporum gypseum | (Mi.gyp.) |
| 10 | Candida albicans | (C.alb.) |
| | Candida tropicalis | (C.trop.) |
| | Aspergillus fumigatus | (Asp.fu.) |
| | Mucor mucedo plus | (Mu.mu ⁺) |
| | Mucor mucedo minus | (Mu.mu ⁻) |
| 15 | Absidia ramosa | (Abs.ra.) |

The minimum inhibitory concentration (MIC) was determined in serial dilution tests in test tubes. The volume of the liquid nutrient medium in each test tube was 4.5 ml.

20 The substances were dissolved in DMSO and diluted with sterile distilled water to 10 concentrations (100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39 and 0.19 µg/ml). 0.5 ml of each of these dilution steps was added to the liquid nutrient medium. Thus, a constant concentration of solvent in all the nutrient media was ensured, irrespective of the active compound concentration.

25 A comparison solution which contained only the solvent in appropriate concentration was included when carrying out each of the tests.

30 The individual strains were maintained on Sabouraud/beerwort agar slants and, before they were used in a test, they underwent a passage on a modified Sabouraud liquid nutrient medium. The strains were then harvested, washed and converted into a suspension of McFaerland 3. 35 in the case of yeasts and molds and of McFaerland 4 - 5 in the case of dermatophytes.

The amount of material inoculated (inoculum) was 100 µl/test tube (inoculated densities: yeasts about

The pH of the liquid nutrient medium was 6.0. After inoculation had taken place the fungi were incubated at 22°C for 14 days.

The MIC was then determined. The concentration step at which growth was no longer visible on macroscopic inspection was used for the determination of the MIC. The comparison substance used was 1-(2-(2,4-dichlorophenyl)-2-(2,4-dichlorophenylmethoxy)ethyl)-1H-imidazole as nitrate (compound A).

10 TABLE II MIC values (µg/ml)

| | Compound | Tri. | Tri. | Tri. | Mi. | Ep. | Mi. | C. | Asp. | Mu. | Mu. | Abs. |
|----|----------|------|------|------|------|------|------|------|------|------|------|------------|
| | No. | me. | ru. | ve. | can | flo | gyp | alb. | trop | fu. | mut | mu- ra. |
| | 3 | 0,78 | 0,78 | 0,78 | 0,78 | 0,78 | 0,78 | 3,12 | 3,12 | 6,25 | 3,12 | 3,12 6,25 |
| | 4 | 1,56 | 1,56 | 1,56 | 6,25 | 1,56 | 0,78 | 6,25 | 6,25 | 6,25 | 6,25 | 6,25 12,5 |
| 15 | 5 | 6,25 | 6,25 | 6,25 | 12,5 | 12,5 | 6,25 | 25,0 | 12,5 | 12,5 | 12,5 | 12,5 25,0 |
| | 6 | 6,25 | 3,12 | 3,12 | 3,12 | 6,25 | 3,12 | 6,25 | 6,25 | 12,5 | 12,5 | 12,5 12,5 |
| | 16 | 25,0 | 1,56 | 1,56 | 3,12 | 3,12 | 3,12 | 6,25 | 3,12 | 3,12 | 6,25 | 3,12 12,5 |
| | 17 | 0,78 | 0,78 | 0,78 | 3,12 | 0,78 | 0,78 | 12,5 | 12,5 | 0,78 | 0,78 | 3,12 6,25 |
| | 18 | 6,25 | 0,78 | 0,39 | 6,25 | 3,12 | 3,12 | 12,5 | 6,25 | 12,5 | 12,5 | 12,5 6,25 |
| 20 | 19 | 0,39 | 0,19 | 0,39 | 0,39 | 0,19 | 0,39 | 0,78 | 0,78 | 1,56 | 1,56 | 1,56 |
| | 20 | 12,5 | 0,19 | 0,39 | 1,56 | 6,25 | 3,12 | 3,12 | 1,56 | 3,12 | 12,5 | 25,0 3,12 |
| | 23 | 0,39 | 0,39 | 0,30 | 1,56 | 0,78 | 0,39 | 3,12 | 1,56 | 1,56 | 6,25 | 6,25 3,12 |
| | 26 | 3,12 | 3,12 | 3,12 | 12,5 | 3,12 | 3,12 | 6,25 | 6,25 | 12,5 | 6,25 | 12,5 12,5 |
| | 27 | 3,12 | 1,56 | 1,56 | 0,78 | 3,12 | 3,12 | 3,12 | 6,25 | 0,78 | 6,25 | 3,12 6,25 |
| 25 | 36 | 6,25 | 6,25 | 6,25 | 1,56 | 1,56 | 6,25 | 3,12 | 0,78 | 25,0 | 6,25 | 6,25 50,0 |
| | 38 | 0,78 | 3,12 | 6,25 | 12,5 | 0,78 | 3,12 | 6,25 | 3,12 | 6,25 | 0,78 | 3,12 6,25 |
| | 6 | 6,25 | 3,12 | 3,12 | 12,5 | 3,12 | 3,12 | 6,25 | 25 | 6,25 | 12,5 | 25 12,5 |
| | 11 | 6,25 | 3,12 | 6,25 | 6,25 | 6,25 | 3,12 | 12,5 | 6,25 | 12,5 | 25 | 6,25 |
| | 24 | 0,10 | 0,10 | 0,10 | 0,78 | 0,10 | 0,39 | 3,12 | 3,12 | 0,39 | 3,12 | 3,12 12,5 |
| 30 | 14 | 0,78 | 1,56 | 0,78 | 6,25 | 0,78 | 3,12 | 12,5 | 12,5 | 3,12 | 6,25 | 6,25 50 |
| | 41 | 3,12 | 1,56 | 1,56 | 1,56 | 3,12 | 1,56 | 3,12 | 12,5 | 3,12 | 3,12 | 3,12 3,12 |
| | 31 | 12,5 | 3,12 | 3,12 | 25 | 3,12 | 6,25 | 12,5 | 25 | 12,5 | 12,5 | 12,5 2,5 |
| | A | 1,56 | 6,25 | 6,25 | 6,25 | 1,56 | 3,12 | 12,5 | 12,5 | 3,12 | 12,5 | 12,5 12,5 |

Example F

Determination of the lethal dose of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-chlorophenylthio)propylamino)ethyl)-1H-imidazole dihydrochloride (compound No. 19) in mice and rats on administration once.

In each case, oral doses of 0, 500, 1,000 and 3,000 mg/kg of body weight were administered to four groups of female and male animals.

10 (Control: double-distilled water)

The following clinical signs were observed.

Mice: Inactivity, convulsions

Rats: Inactivity, ruffled fur, convulsions

Mice LD₁₀₀

15 female >1,000 mg/kg <3,000 mg/kg

male > 500 mg/kg <1,000 mg/kg

Rats

female > 500 mg/kg <1,000 mg/kg

male >1,000 mg/kg <3,000 mg/kg

20 Example G

Determination of the LD₅₀ of 1-(2-(2,4-dichlorophenyl)-2-(3-(4-chlorophenylthio)propylamino)ethyl)-1H-imidazole dihydrochloride (compound No. 19) in mice and rats by i.v. administration. In each case, 0 (0.9% NaCl solution), 12.5, 25.0, 50.0 and 100 mg/kg of body weight were injected i.v. into 5 groups of female and male animals.

The following clinical signs were observed

Mice: Inactivity, necrotic tail

30 Rats: Inactivity, necrotic tail, convulsions

LD₅₀

Mice

female 84.1 (20.8 - 340.0) mg/kg

male 42.0 (13.9 - 127.5) mg/kg

35 Rats

female 56.1 (35.4 - 89.1) mg/kg

male 70.7 mg/kg

Example H

Compound No. 19 was investigated for its potential to cause gene mutations in five *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.

5

The following concentrations were tested, both with metabolic activator (S 9 mix) and without metabolic activator.

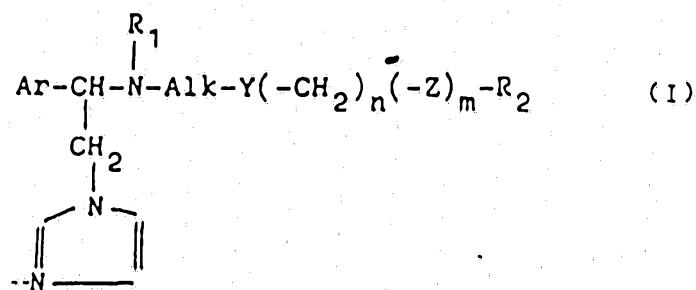
10

I: 10, 33.3, 100.0, 333.3, 1,000 µg/plate
II: 3.3, 10, 33.3, 100, 333.3 µg/plate

No mutagenic activity whatever was observed, either with or without metabolic activator.

Patent Claims The claims defining the invention are as follows:

1. An imidazole derivative of the formula

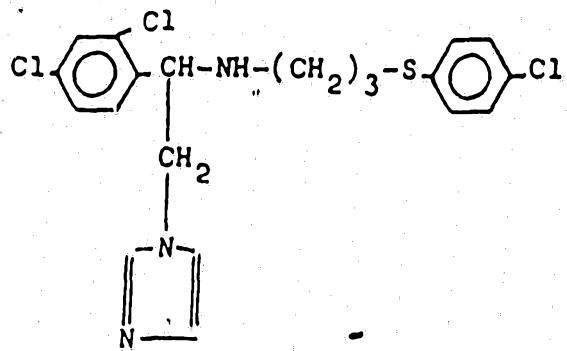


in which Ar denotes phenyl, biphenyl, naphthyl or thienyl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, R₁ denotes hydrogen or lower alkyl, Alk denotes straight-chain or branched alkylene having 1 to 10 carbon atoms, Y denotes oxygen, sulfur, sulfinyl or sulfonyl, n denotes one of the numbers 0, 1 or 2, Z denotes sulfur or sulfinyl, m denotes the number 0 or 1, m being the number 0 when Y denotes sulfur, sulfinyl or sulfonyl, and m being the number 1 when Y denotes oxygen, and R₂ denotes cyclohexyl, or denotes phenyl or naphthyl, each of which is optionally substituted by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy, or denotes biphenyl or pyridyl, and its pharmaceutically acceptable acid addition salts.

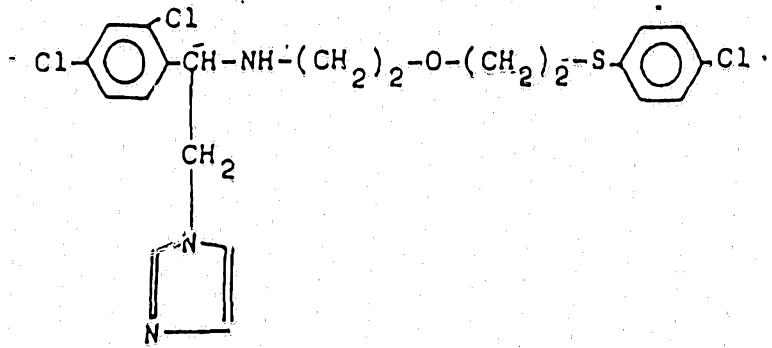
2. An imidazole derivative as claimed in claim 1, of the formula I in which R₁ denotes a hydrogen atom or the methyl radical, Ar denotes 2,4-dichlorophenyl or 4-chlorophenyl, Alk denotes straight-chain or branched alkylene having 1 to 6 C atoms, Y denotes sulfur, sulfinyl or sulfonyl, Z denotes sulfur or sulfinyl, and R₂ denotes cyclohexyl, phenyl, 4-methylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 2,6-dichlorophenyl or naphthyl.

3. An imidazole derivative as claimed in claim 1, selected from the following

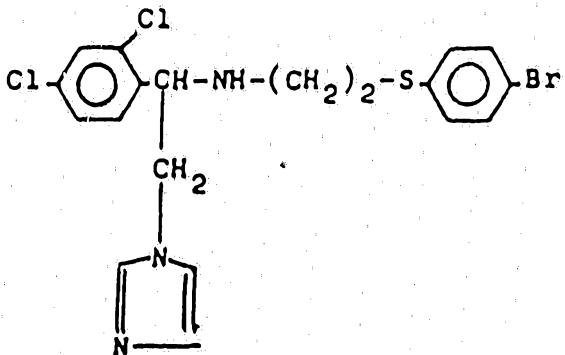
1-(2-(2,4-dichlorophenyl)-2-(3-(4-chlorophenylthio)-
propylamino)ethyl)-1H-imidazole



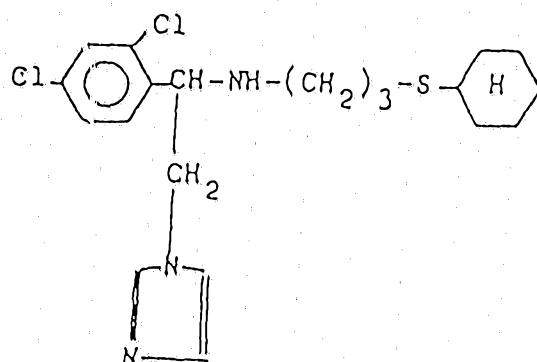
1-(2-(2,4-dichlorophenyl)-2-(2-(4-chlorophenylthio)-
ethoxyethylamino)ethyl)-1H-imidazole



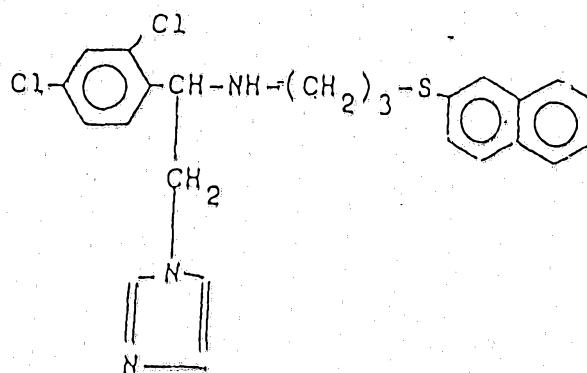
1-(2-(2,4-dichlorophenyl)-2-(2-(4-bromophenylthio)ethyl-
amino)ethyl)-1H-imidazole



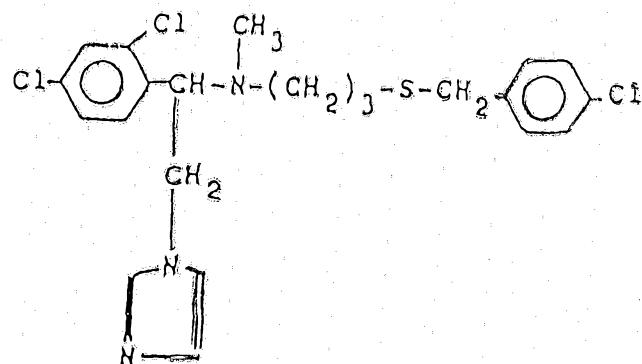
1-(2-(2,4-dichlorophenyl)-2-(3-cyclohexylthiopropylamino)-
ethyl)-1H-imidazole



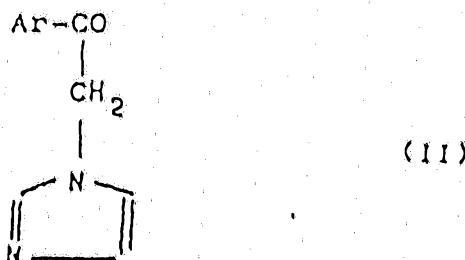
1-(2-(2,4-dichlorophenyl)-2-(3-(2-naphthylthio)propylamino)ethyl)-1H-imidazole



1-(2-(2,4-dichlorophenyl)-2-(N-methyl-3-(4-chlorobenzylthio)propylamino)ethyl)-1H-imidazole



4. A process for the preparation of a compound of the formula I according to any one of claims 1 to 3, which comprises reacting a compound of the formula II



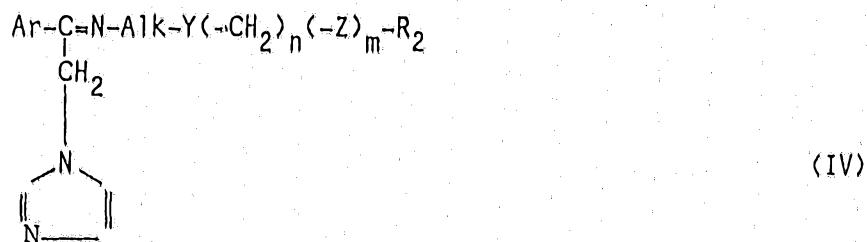
(III)



in which Ar denotes phenyl, biphenyl, naphthyl or thiophenyl, each of which is optionally substituted by halogen, lower alkyl or lower alkoxy, with a compound of the formula III.



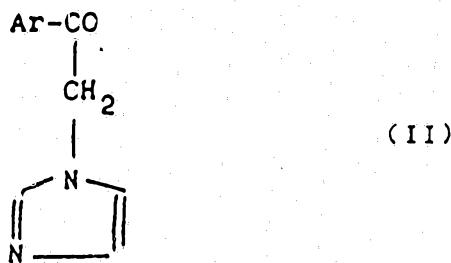
in which R_2 denotes cyclohexyl, σ^* denotes phenyl or naphthyl, each of which is optionally substituted by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy, or denotes biphenyl or pyridyl, Z denotes sulfur or sulfinyl, Y denotes oxygen, sulfur, sulfinyl or sulfonyl, m denotes the number 0 or 1, m being the number 0 when Y denotes sulfur, sulfinyl or sulfonyl, and m being the number 1 when Y denotes oxygen, n denotes one of the numbers 0, 1 or 2, Alk denotes straight-chain or branched alkylene having 1 to 10 carbon atoms, where appropriate in the presence of an inert diluent, reducing the resulting imino compound of the formula IV



in which Ar, Alk, Y, Z, R_2 , n and m have the above meaning, where appropriate in the presence of an inert diluent, and, if desired, converting the resulting compound of the formula I in which R_1 denotes hydrogen, by customary alkylation methods, into a compound of the formula I in which R_1 denotes lower alkyl.

5. A process for the preparation of a compound of the formula I according to any one of claims 1 to 3, which comprises reacting a compound of the formula II

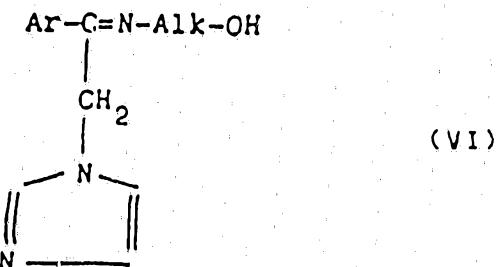




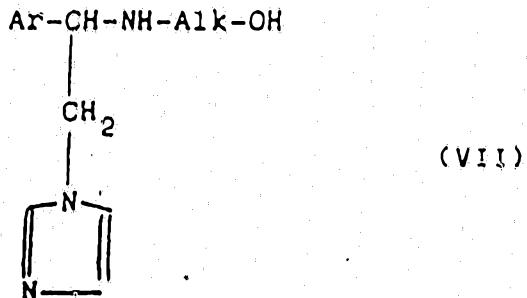
with an aminoalkanol of the formula V



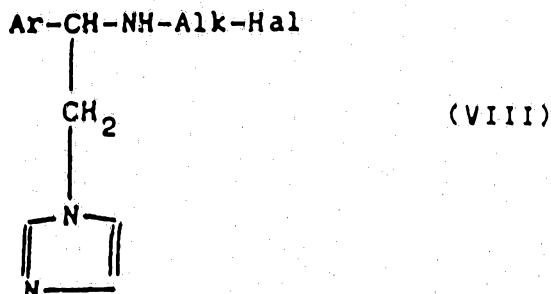
reducing the imino compound which is obtained as reaction product, of the formula VI



converting the resulting hydroxyalkylamino compound of the formula VII



into the corresponding halogenoalkylamino compound of the formula VIII



reacting the latter with a compound of the formula IX



and, if desired, converting the resulting compound of the formula I in which R_1 denotes hydrogen, by customary alkylation methods, into a compound of the formula I in which R_1 denotes lower alkyl, where Ar, Alk, Y, Z, R_2 , X, n and m in the above formulae V to IX have the meaning indicated for formula I, and Hal represents halogen.

6. An antimycotic agent which contains at least one compound of the formula I as claimed in claim 1.

7. A process for the preparation of an antimycotic agent, which comprises mixing a compound of the formula I with pharmaceutically acceptable vehicles and/or auxiliaries.

8. The use of a compound of the formula I for the preparation of an antimycotic agent.

9. An imidazole derivative substantially as hereinbefore described with reference to any one of Compounds 1 to 41.

10. A process for the preparation of an imidazole derivative, said process being substantially as hereinbefore described with reference to Example 1a and 1b, Example 2a and 2b or Example 3.

DATED this FIFTH day of DECEMBER 1989

CL Pharma Aktiengesellschaft

Patent Attorneys for the Applicant

SPRUSON & FERGUSON

