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Naito et al.

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[54] **AZOLYLAMINE DERIVATIVE**

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[21] Appl. No.: **781,204**

[22] Filed: **Jan. 9, 1997**

Related U.S. Application Data

[62] Division of Ser. No. 532,800, filed as PCT/JP94/00737, May 2, 1994, Pat. No. 5,620,994.

[30] **Foreign Application Priority Data**

May 10, 1993 [JP] Japan 132931

[51] **Int. Cl.**[6] **A61K 31/445**; C07D 401/06; C07D 403/06

[52] **U.S. Cl.** **514/326**; 540/603; 546/210; 548/314.7; 514/212; 514/397

[58] **Field of Search** 546/210; 548/314.7; 514/326, 397, 212; 540/603

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,507,484 3/1985 Gymer et al. .

FOREIGN PATENT DOCUMENTS

0 054 974 A1 6/1982 European Pat. Off. .
2 159 148 11/1985 United Kingdom .

Primary Examiner—Patricia L. Morris
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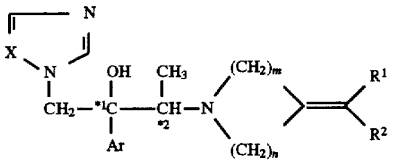
[57] **ABSTRACT**

There is disclosed a fungicide containing, as an effective ingredient, a compound having the general formula (I):



(I)

or an acid addition salt thereof, particularly the compound wherein an absolute configuration of the asymmetric carbon atoms is R,R-configuration or an acid addition salt thereof.

9 Claims, No Drawings

AZOLYLAMINE DERIVATIVE

This is a division of application Ser. No. 08/532,800 filed Nov. 7, 1995, which is a U.S. national stage under §371 of application No. PCT/JP94/00737 filed May 2, 1994, claiming priority from Japanese patent application No. 132931 filed May 10, 1993.

TECHNICAL FIELD

The present invention relates to an azolylamine which is effective for treatment for mycosis in human and animals and useful as fungicides for agricultural and horticultural use or industrial use.

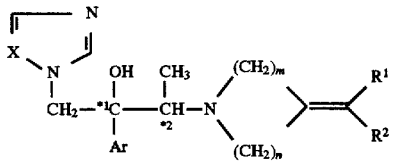
BACKGROUND ART

Azolylamine derivatives having, in the molecule, both of an azolyl group such as triazolyl group or imidazolyl group and a cyclic amino group such as piperidino group, pyrrolidino group or morpholino group are described in JP-A (Japanese Unexamined Patent Publication)-140788/1982 and GB-A-2159148. However, it is hard to say in the aspect of an antifungal action etc. that each compound has sufficient efficacy as a medicament. Furthermore, any compound having methylene group or a substituted methylene group on the cyclic amino group is not disclosed therein.

The present invention provides a novel azolylamine derivative showing the potent antifungal activity which is characterized by having methylene group or a substituted methylene group on the cyclic amino group.

DISCLOSURE OF THE INVENTION

The present invention provides a compound having the general formula (I):



(I)

wherein Ar is non-substituted phenyl group or a phenyl group substituted with 1 to 3 substituents selected from a halogen atom and trifluoromethyl,

R^1 and R^2 are the same or different and are hydrogen atom, a lower alkyl group, a non-substituted aryl group, an aryl group substituted with 1 to 3 substituents selected from a halogen atom and a lower alkyl group, an alkenyl group, an alkynyl group or an aralkyl group,

m is 2 or 3,

n is 1 or 2,

X is nitrogen atom or CH, and

*1 and *2 mean an asymmetric carbon atom,

or an acid addition salt thereof.

As the above-mentioned compound having the general formula (I), there are particularly preferable the compound wherein absolute configuration of the asymmetric carbon atoms with *1 and *2 is R,R-configuration, and the compound being a mixture containing the compound having the general formula (I) wherein the absolute configuration of the asymmetric carbon atoms with *1 and *2 is R,R-configuration or an acid addition salt thereof and other optical isomer.

The present invention also provides a fungicide containing the above-mentioned compound having the general formula (I) or an acid addition salt thereof as an effective ingredient, and a process for treating mycosis using the above-mentioned compound.

BEST MODE FOR CARRYING OUT THE INVENTION

In the above-mentioned general formula (I), the substituted phenyl group is a phenyl group having 1 to 3 substituents selected from a halogen atom and trifluoromethyl, and includes, for instance, 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 4-trifluoromethylphenyl, 2-chloro-4-fluorophenyl, 4-bromophenyl or the like.

The lower alkyl group includes, for instance, a straight chain, branched chain or cyclic alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and tert-pentyl.

The non-substituted aryl group includes, for instance, phenyl, naphthyl, biphenyl, or the like.

The substituted aryl group includes, for instance, 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 4-trifluoromethylphenyl, 2-chloro-4-fluorophenyl, 4-bromophenyl, 4-tert-butylphenyl, 4-nitrophenyl, or the like.

The alkenyl group includes, for instance, vinyl, 1-propenyl, styryl, or the like.

The alkynyl group includes, for instance, ethynyl, or the like.

The aralkyl group includes, for instance, benzyl, naphthylmethyl, 4-nitrobenzyl, or the like.

The compound of the present invention having the general formula (I) contains at least two asymmetric carbon atoms in the molecule, and there exsist an optical isomer and a diastereomer. With respect to the optical isomer, both enantiomers can be obtained according to the general procedure of optical resolution or asymmetric synthesis. A separation of the diastereomer can be carried out according to the usual separation procedure such as a fractional recrystallization or a chromatography to give each isomer. The compound having the general formula (I) includes one of these isomers or a mixture thereof.

Among these, the compound wherein an absolute configuration of the asymmetric carbon atoms is R,R-configuration, has particularly potent antifungal action and therefore it is preferably used particularly.

Representative examples of the compound of the present invention having the general formula (I) include, for instance,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino-1-(1H-1,2,4-triazol-1-yl)butane-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butane-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-yl)-1-(1H-imidazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2R,3R)-2-(4-chlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(4-chlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(4-chlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(4-chlorophenyl) -3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2S,3S)-2-(4-chlorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(4-chlorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2R,3R)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2S,3S)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(4-trifluoromethylphenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-dichlorophenyl)-3-(4-methylenepiperidino)-1-(1H-imidazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-ethylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-ethylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-ethylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-propylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-propylidenepiperidino) -1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-propylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-n-butylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-n-butylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-n-butylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-n-pentylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-n-pentylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-n-pentylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-n-hexylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-n-hexylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-n-hexylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-cyclopropylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-cyclopropylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-cyclopropylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-cyclohexylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-cyclohexylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-cyclohexylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-benzylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-benzylidenepiperidino) -1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS),2-(2,4-difluorophenyl)-3-(4-benzylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2,-(2,4-difluorophenyl)-3-(4-isopropylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-isopropylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-isopropylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-diphenylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-diphenylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2RS,3RS)- 2-(2,4-difluorophenyl)-3-(4-diphenylmethylenepiperidino)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-propenylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-propenylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS),2-(2,4-difluorophenyl)-3-(4-propenylidenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(4-propenylidenepiperidino)- 1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(4-propylidenepiperidino) -1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(4-propynylidenepiperidinol)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(3-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(3-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

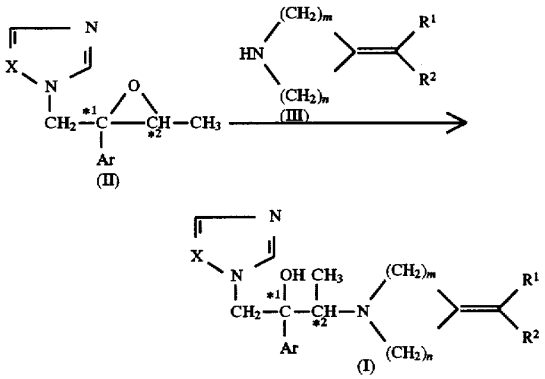
(2RS,3RS)-2-(2,4-difluorophenyl)-3-(3-methylenepiperidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-difluorophenyl)-3-(3-methylenepyrrolidino)-1-(1H-2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-difluorophenyl)-3-(3-methylenepyrrolidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2RS,3RS)-2-(2,4-difluorophenyl)-3-(3-methylenepyrrolidino)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, and the like.

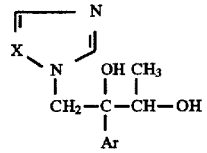
The compound of the present invention having the general formula (I) can be prepared according to the process shown as below:



(In the above-mentioned formulae, Ar, R^1, R^2, X, m and n have the same meanings as defined above.)

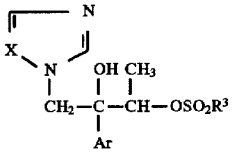
Namely, the reaction of an epoxy compound having the general formula (II) and an amine derivative having the general formula (III) can lead to the compound having the general formula (I).

The epoxy compound having the general formula (II) can be obtained according to such process as is described in JP-A(Japanese Unexamined Patent Publication)-191262/1990 etc., for example, a process wherein a compound having the general formula (IV):



(IV)

wherein Ar and X have the same meanings as defined above, is reacted in the presence of a base with a compound having the formula R^3SO_2—O—SO_2R^3 or R^3SO_2—Z, wherein R^3 is a lower alkyl group, a halogenated lower alkyl group, or a phenyl group which may be substituted, and Z is a leaving group such as a halogen atom, to give a compound (V):



(V)

and then the compound (V) is reacted with a base.

The amine derivative having the general formula (III) can be obtained according to the known synthetic process described in, for example, Chem. Pharm. Bull. 41 (11) 1971–1986 (1993) or processes described in Reference Examples of the present invention.

In case that the amine derivative is in a fore of a salt thereof with an acid such as a base, the amine derivative is used in a form of a free amine by being neutralized previously or in a reaction solution with an inorganic base such as sodium hydroxide or an organic base such as triethylamine.

The reaction is usually carried out using water, an organic solvent or a mixed solution of water and an organic solvent, or in the absence of any solvent. As the organic solvent, a solvent which does not react with a starting compound can be used. For example, an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol, ethylene glycol, propylene glycol, glycerin or methyl cellosolve, an ether such as tetrahydrofuran, dioxane or dimethoxyethane, an amide such as N,N-dimethylformamide or N,N-dimethylacetamide, dimethyl sulfoxide, and the like can be used alone or in a mixture thereof.

In the above-mentioned reaction system, the reaction advances more smoothly by adding 1 to 80 v/v % of water in the mixed solution to the reaction system in comparison with using only an organic solvent.

With respect to an amount of each material in the reaction solution, from 1 to 20 mol of the compound (III) is used per mol of the compound (II).

A reaction temperature is room temperature to 200° C., preferably 50° to 150° C. A reaction time is 1 to 72 hours.

After the end of the reaction, the solvent is removed and then purification is carried out according to a procedure such as a recrystallization or a chromatography. Thereby the compound of the present invention having the general formula (I) is isolated.

The compound of the present invention having the general formula (I) can, if required, form a pharmaceutically acceptable salt thereof, for example, a salt thereof with an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid or hydrobromic acid, and a salt thereof with an organic acid such as fumaric acid, maleic acid, acetic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid or toluenesulfonic acid.

Then, the antifungal activity of the compound of the present invention having the above-mentioned general formula (I) is described. Test compound number used in the following tests was referred to the example number described below.

1. Determination of the minimum inhibitory concentration (MIC)

MIC of a test compound against *Candida albicans* ATCC-10259 was determined by the both dilution method employing synthetic amino acid medium (SAAMF medium). Namely, to 3 μl of twofold dilution series of solution containing the test compound was added 300 μl of SAAMF medium inoculated with the fungus at the final concentration of 1×10^3 cells/ml. After thus obtained mixture was incubated at 35° C. for 2 days, MIC was determined by examining a

minimum concentration of the test compound in which concentration the test compound inhibited the growth of the fungus. MIC of a test compound against the fungus other than the *Candida albicans* was determined by the agar dilution method employing Sabouraud's agar medium. That is to say, a test compound was dissolved in dimethyl sulfoxide to give a solution containing the test compound in the concentration of 10 mg/ml. Further, thus obtained solution was diluted with dimethyl sulfoxide according to two-fold dilution series and 0.1 ml of the diluted solution was taken into a sterile shale. After 9.9 ml of Sabouraud's agar medium was added thereto, the mixture was sufficiently mixed to give a drug-added plate. The plate was inoculated with 5 μl of a fungus suspension at 10^6cells/ml by Microplanter (Sakuma Seisakusho Co., Ltd.). As to *Aspergillus fumigatus* NI-5561 and *Cryptococcus neoformans* NI-7496, a plate was incubated at 30° C. for 48 hours. As to *Trichophyton mentagrophytes* KD-01, a plate was incubated at 30° C. for 7 days. After incubation, MIC was determined by examining a minimum concentration of a test compound in which concentration the test compound inhibited the growth of the fungus. The results thereof are shown in Table 1. Clotrimazole and fluconazole were used as comparative control compounds.

The abbreviated designation of names of the test fungi is as follows:

Name of fungus	Abbreviated designation
Candida albicans ATCC 10259	C.a.
Cryptococcus neoformans NI-7496	Cr.n.
Aspergillus fumigatus NI-5561	A. f.
Trichophyton mentagrophytes KD-01	T.m.

The antifungal activity (the minimum inhibitory concentration MIC) of the compound of the present invention in the Examples against each fungus is shown in Table 1.

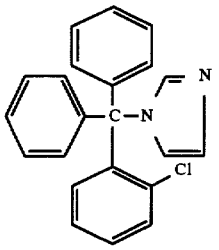
TABLE 1

Test compound	Minimum inhibitory concentration (MIC (μg/ml) Test fungus			
(Ex. No.)	C.a.	Cr.n.	A.f.	T.m.
1	<0.025	0.05	0.05	0.39
2	<0.025	0.1	0.1	0.39
3	0.39	0.78	>100	50
4	<0.025	<0.025	0.05	<0.025
5	<0.025	0.025	0.05	0.1
6	<0.0125	0.2	6.25	3.13
7	0.025	0.05	0.39	0.39
8	<0.025	0.1	0.2	0.78
10	<0.025	0.025	0.1	0.39
12	<0.025	0.1	0.2	0.78
13	0.1	0.39	0.78	1.56
14	<0.025	0.39	0.39	0.78

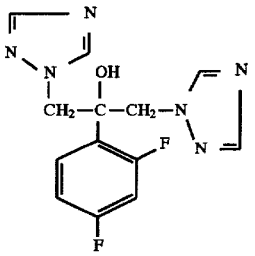
TABLE 1-continued

Test compound	Minimum inhibitory concentration (MIC (μg/ml) Test fungus			
(Ex. No.)	C.a.	Cr.n.	A.f.	T.m.
Clotrimazole	0.025	0.2	0.78	0.39
Fluconazole	0.39	12.5	>100	>100

Clotrimazole



Fluconazole



The above-mentioned results reveal that the compound of the present invention having the general formula (I), especially the compound wherein the absolute configuration is R,R-configuration, has extremely high activity in comparison with conventional fungicides.

Furthermore, compared to Clotrimazole and fluconazole, it is found that the compound of the present invention, i.e. the compound wherein a cyclic amino group having methylene group is bonded, has surprisingly high activity.

2. Test on treatment for infection

(1) Effect on trichophytosis in guinea pigs.

In the back of male Hartley guinea pig, weighing 400 to 500 g, a portion of skin was unhaired and rubbed lightly with sandpaper, to which 0.1 ml of microconidium suspension of *Trichophyton mentagrophytes* KD-04 (10^7 cells/ml) was dropped and the skin surface was infected by rubbing it with a glass rod. The test compound was dissolved in polyethylene glycol 400-ethanol (75:25) so as to give a 1% solution thereof and 0.2 ml of the resultant solution was applied for treatment once a day for 10 days from 3 days after the infection. The animal was killed by etherization 2 days after the last treatment and 10 tissue specimens of skin were cut out from the infected portion and incubated on Sabouraud's agar medium for 7 days. Inhibitory ratio was calculated according to the following formula:

Inhibitory ratio (%)={1-(number of tissue specimens found fungi/total number of tissue specimens)}×100

The results are shown in Table 2. Clotrimazole was used as a control compound.

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