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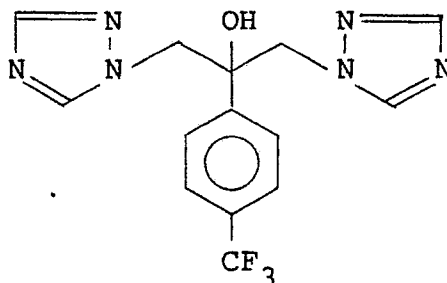
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54 Triazole compound, antimycotic preparation containing same, and method for the prevention and/or treatment of deep-seated mycosis by using same.

57 Disclosed herein is 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):



(I)

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An antimycotic preparation containing the triazole compound (I) is also disclosed. Also disclosed is a method for the prevention and/treatment of a deep-seated mycosis of a human or mammal, which comprises administering an effective dose of the triazole compound (I) to the the human or mammal.

TRIAZOLE COMPOUND, ANTIMYCOTIC PREPARATION CONTAINING SAME, AND METHOD FOR THE PREVENTION AND/OR TREATMENT OF DEEP-SEATED MYCOSIS BY USING SAME

BACKGROUND OF THE INVENTION

5 1) Field of the Invention:

This invention relates to a novel triazole compound having excellent antimycotic activities and high safety in combination, an antimycotic preparation containing same as an active ingredient, and a method for the prevention and/or treatment of a deep-seated mycosis by using same.

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2) Description of the Related Art:

15 Mycoses include skin diseases represented by various trichophytoses, eczema marginatum, psoriasis and cutaneous candidiasis as well as deep-seated mycoses typified by fungal meningitis, fungal infectious inspirator disease, fungemia and urinary tract mycosis.

Of these, deep-seated mycoses cannot be treated with conventional antibiotics or chemotherapeutic agents. There is an observable tendency to increased patients suffering from these diseases. There has accordingly a strong desire for the development of a drug effective for the treatment of these diseases.

20 Only a few therapeutic agents have heretofore been used, including polyene antibiotics such as nystatin and amphotericin B, azole compounds such as miconazole, and pyrimidine compounds such as flucytosine.

25 These drugs are however not fully satisfactory, because they are accompanied by the problem that instillation is only feasible for administration due to toxicity or the like or even if oral administration is possible problems arise in the kidneys, bone marrow, stomach and/or the like or the antimycotic spectrum is narrow.

Ketoconazole, fluconazole and the like have been studied and developed recently as azole drugs for the treatment of deep-seated mycoses. However, these azole compounds include very few compounds which can exhibit antimycotic activities when administered by a simple method such as oral administration. Under the circumstances, it is not believed to be too much to say that it is only fulconazole that has potential utility as a medicine in practice. Fluconazole is disclosed in U.S. Patent No. 4,404,216.

30 However, this fulconazole is not free of the problem of side effects and can hardly be regarded satisfactory from the standpoint of safety.

There has hence been a desire for the development of a compound having antimycotic activities equal to or higher than fulconazole and moreover having higher safety than fulconazole upon administration.

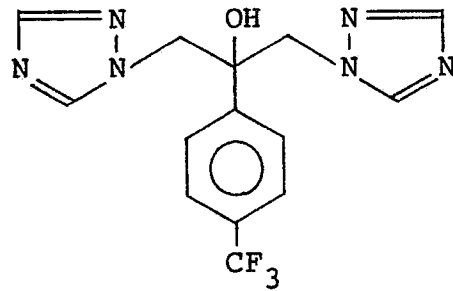
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SUMMARY OF THE INVENTION

40 Under the above-described circumstances, the present inventors have synthesized numerous compounds and have also conducted an investigation on their pharmacological effects. As a result, it has now been found that the triazole compound represented by the formula (I) set out below has excellent specific antimycotic activities and a high level of safety and is extremely useful as an antimycotic agent.

45 In one aspect of this invention, there is thus provided 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):

50



(I)

In another aspect of this invention, there is also provided an antimycotic preparation comprising as an active ingredient the triazole compound (I).

In a further aspect of this invention, there is also provided a method for the prevention and/treatment of a deep-seated mycosis of a human or mammal, which comprises administering an effective dose of the triazole compound (I) to the human or mammal.

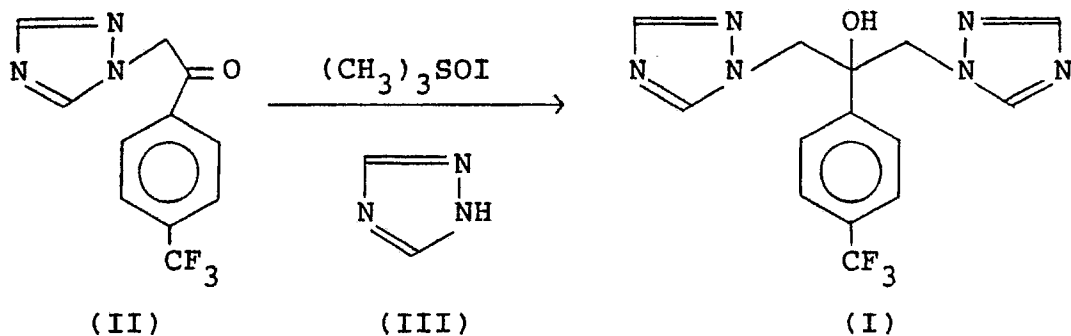
The triazole compound (I) according to this invention exhibits more specific antimycotic activities compared to similar compounds as will be readily understood from a referential test which will be described herein. As will also be demonstrated in the same referential test, its apothanasia effects upon oral administration are greater than fluconazole whose development as an oral preparation is now under way. Furthermore, body weight reductions were observed after administration in a group administered with fluconazole, thus indicating the existence of side effects. In contrast, the body weight increased steadily in a group administered with the triazole compound (I) of this invention. It is therefore evident that the triazole compound (I) of this invention is far superior in safety to fluconazole.

In addition, the acute toxicity of the triazole compound (I) according to this invention is 1,200 mg/kg in terms of LD₅₀ (mice; P.O.). It is therefore possible to effectively and safely treat and/or prevent a deep-seated mycosis of human or a mammal such as a dog, cat, horse, cow, pig, sheep or monkey, said deep-seated mycosis being induced by infection or by a fungus existing in the body, by oral administration of the compound.

DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Some compounds similar to 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol (hereinafter abbreviated as the "triazole compound") of this invention have already been disclosed in U.S. Patent No. 4,416,682. However, the triazole compound of this invention is not specifically disclosed in the above prior art publication and is hence novel.

The triazole compound of this invention can be easily synthesized by any one of the processes disclosed in the prior art publication, for example, by the process represented by the following equation:



Namely, the triazole compound (I) can be prepared by reacting 2-(1,2,4-triazol-1-yl)-4'-trifluoromethylacetophenone (II) and 1,2,4-triazole (III) at room temperature or under reflux conditions, for one to several tens hours, in the presence of trimethylsulfoxonium iodide and an alkali, in an alcohol such as t-butanol.

The target triazole compound (I) can be obtained in a substantially pure form by distilling out the solvent from the reaction mixture after completion of the reaction, adding water to the residue, extracting the resultant mixture with a solvent such as ethyl acetate, washing the extract thus obtained and then distilling out the solvent. The resultant compound may then be subjected to purification such as column chromatography or recrystallization as needed, thus obtaining the target compound in a purified form.

If necessary, the triazole compound obtained as described above can be converted into a salt such as the hydrochloride, nitrate, hydrobromide, sulfate, p-toluenesulfonate, methanesulfonate, fumarate, maleate, succinate or lactate.

When the triazole compound of this invention is orally administered as an antimycotic agent, the dose varies depending on the patient's weight, age, sex and conditions, the preparation form, etc. In general, it is however suitable to administer about 5-1,000 mg of the triazole compound in the case of oral administration and about 1-500 mg of the triazole compound in the case of parenteral administration, both per day and per human adult, in 1-4 portions.

It is preferable to administer the antimycotic agent of this invention orally in the form of tablets, granules, powder, capsules or suspension prepared in a manner known per se in the art. However, it can also be administered parenterally in the form of an injection. To produce a solid preparation for oral administration, the triazole compound (I) is added with an excipient and optionally with a binder, a disintegrator, a lubricant, a colorant, a corrigent, an extender, a coating agent, a sugar coating material and/or the like, followed by formation into tablets, granules, powder, capsules or the like by a method known per se in the art. To prepare an injection on the other hand, the triazole compound (I) is optionally dissolved in an oil such as olive oil or sesame oil and is then formulated into a subcutaneous or intramuscular injection. As an alternative, a surfactant or the like is added to formulate a so-called solubilized preparation.

The present invention will hereinafter be described in further detail by the following examples, tests and preparation example. It should however be borne in mind that the present invention is not limited to or by them.

Example:

In 10 ml of t-butanol were dissolved 1.02 g of 2-(1,2,4-triazol-1-yl)-4'-trifluoromethylacetophenone, 2.28 g of trimethylsulfoxonium iodide, 1.20 g of potassium hydroxide and 0.33 g of 1,2,4-triazole. The resultant mixture was stirred at 70 °C for 16 hours. After completion of the reaction, the solvent was distilled out, water was added to the residue, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and then dried over anhydrous magnesium sulfate. The solvent was thereafter distilled out. Using chloroform, the residue was purified by chromatography on a silica gel column to obtain 0.69 g of the triazole compound (I) as colorless crystals (yield: 51%).

Melting point: 170-172 °C.

IR (KBr), cm^{-1} : 3230, 1620, 1507, 1320.

NMR (δ ppm in CDCl_3): 4.55 (4H,s), 7.20-7.85 (4H, m), 7.92 (2H,s), 8.02 (2H,s).

Test 1:

Antimycotic activities:

Male ICR mice of 4 weeks old were used as groups, each consisted of 5 mice. Each mouse was inoculated at caudal vein with 2.8×10^6 cells of Candida albicans. From one hour after the inoculation, each test compound was dissolved in 0.5 ml of 0.06 N hydrochloric acid which had been added with "0.2% TO-10M" (trade name; product of Nikko Chemicals Co., Ltd.) and was orally administered once a day, four times in total. The mice were observed until the 14th day after the inoculation of the fungus. The average survival days of each group was compared with those of the control group to determine T/C (%). The results are summarized in Table 1.

$$T/C (\%) = \frac{\text{Average survival days of group administered with test compound}}{\text{Average survival days of control group}}$$

5

Table 1

10

Test compound	Dose (mg/kg)	T/C (%)
Triazole compound (I)	5	450
	2.5	385
	1.25	186
Fluconazole (control drug)	5	443
	2.5	379
	1.25	143
Control	-	100

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Referential Test:

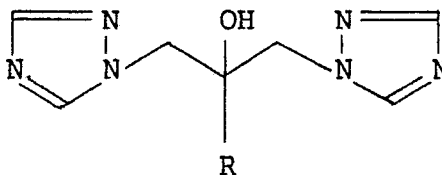
30 Antimycotic activities:

In a manner similar to Test 1, antimycotic activities of each of the test compounds shown below in Table 2 were investigated. As will be readily envisaged from the results, practically no antimycotic activities were observed from the oral administration of those compounds.

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Test compounds:

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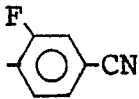

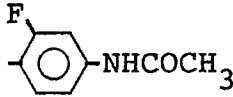
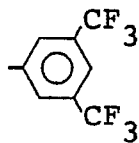
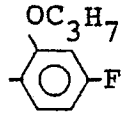
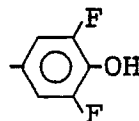
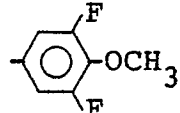
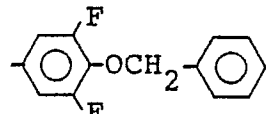
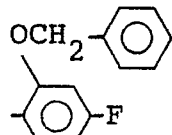


(A)

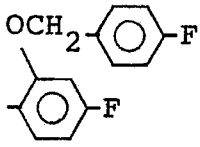
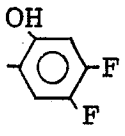
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	R in formula (A)	Dose (mg)	T/C
5		40	81
10		40	136
15		40	82
20		20	118
25		40	125
30		40	82
35		40	91
40		40	73
45		40	122
50			

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R in formula (A)	Dose (mg)	T/C
	40	117
	40	125

Test 2:

Measurement of body weight variations:

With respect to the laboratory animals administered with 2.5 mg/Kg of the respective test compounds in Test 1, body weight variations were investigated along the passage of time. The results are summarized in Table 2.

Table 2

Test compound	Triazole compound (I)	Fluconazole
Days after administration		
0	21.0 g	21.0 g
1	20.6	20.2
2	21.4	20.6
3	22.2	20.4
4	23.0	20.8
5	23.3	20.4
6	23.1	19.4

Preparation Example 1:

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Tablets :	
Triazole compound (I)	50 mg
Crystalline cellulose	50 mg
Lactose	50 mg
Hydroxypropylcellulose	18 mg
Magnesium stearate	2 mg
TOTAL	170 mg

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Tablets of the above composition were produced by a method known per se in the art. It is possible to treat those tablets into sugar coated tablets or film coated tablets as needed.

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Preparation Example 2:

Capsules :	
Triazole compound (I)	50 mg
Light anhydrous silicic acid	25 mg
Lactose	100 mg
Starch	50 mg
Talc	25 mg
TOTAL	250 mg

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The above mixture was filled in No. 1 capsules to obtain capsules.

Preparation Example 3:

Granules :	
Triazole compound (I)	50 mg
Lactose	600 mg
Corn starch	200 mg
Sodium carboxymethylcellulose	20 mg
Hydroxypropylcellulose	130 mg
TOTAL	1,000 mg

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Granules of the above composition were produced by a method known per se in the art.

50 Preparation Example 4:

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Powder :	
Triazole compound (I)	50 mg
Light anhydrous silicic acid	20 mg
Precipitated calcium carbonate	10 mg
Lactose	250 mg
Starch	70 mg
TOTAL	400 mg

Powder of the above composition was produced by a method known per se in the art

15 Preparation Example 5:

Injection :	
Triazole compound (I)	5 mg
Hydrogenated castor oil	85 mg
Propylene glycol	60 mg
Glucose	50 mg
Distilled water for injection,	to total volume of 1 ml

Injection of the above composition was produced by a method known per se in the art.

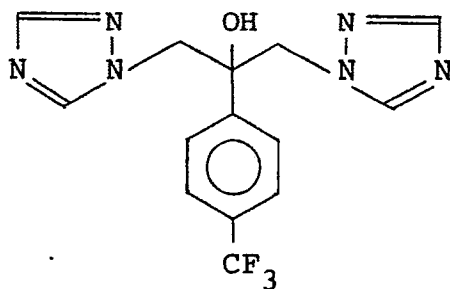
30 Preparation Example 6:

Injection :	
Triazole compound (I)	5 mg
Polyoxyethylene-hydrogenated castor oil	40 mg
Propylene glycol	60 mg
Distilled water for injection,	to total volume 1 ml

Injection of the above composition was produced by a method known per se in the art.

45 **Claims**

1. 1,3-Bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):

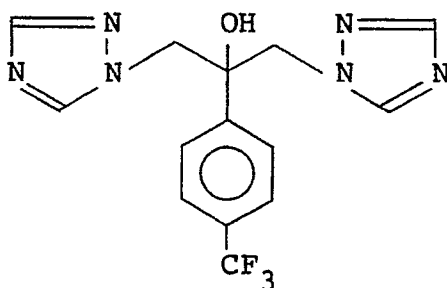


(I)

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2. An antimycotic preparation comprising as an active ingredient 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):



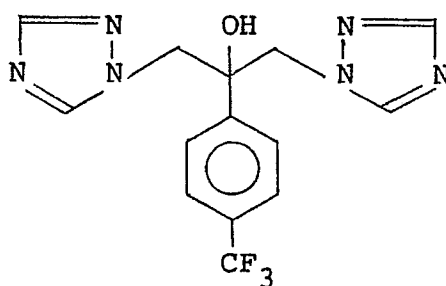
(I)

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3. A method for the prevention and/treatment of a profundus mycosis of a human or mammal, which comprises administering to the human or mammal an effective dose of 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):



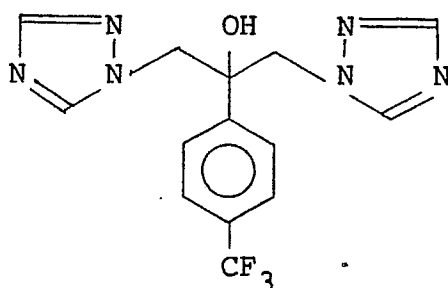
(I)

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4. A use of 1,3-bis(1,2,4-triazol-1-yl)-2-(4-trifluoromethylphenyl)propan-2-ol represented by the following formula (I):



(I)

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for preparing a medicine for the prevention and/or treatment of a deep-seated mycosis of a human or mammal.